CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER(S)

NDA 21-727

Trade Name: OraDisc A
Mucoadhesive Patch, 2 mg

Generic Name(s): (amlexanox)

Sponsor: Access Pharmaceuticals, Inc.

Agent:

Approval Date: September 29, 2004

Indication: Provides for the treatment of aphthous ulcers in adults and adolescents 12 years of age and older (not indicated for use in children below age 12 or in patients with an abnormal immune system)

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APPLICATION NUMBER:

21-727

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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-727

Approval Letter(s)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-727

Access Pharmaceuticals, Inc.
Attention: David P. Nowotnik, Ph.D.
Senior VP, Research & Development
2600 Stemmons Freeway, Suite 176
Dallas, TX 75207-2107

Dear Dr. Nowotnik:

Please refer to your December 4, 2003, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for, TRADENAME (amlexanox) Mucoadhesive Patch, 2 mg.

We acknowledge receipt of your submissions dated December 12, 2003, January 8 and 30, February 3 and 27, March 15 and 24, June 2 and 8, August 13 and 30, September 20 and September 24, 2004 (facsimile).

This new drug application provides for the use of TRADENAME (amlexanox) Mucoadhesive Patch, 2 mg for the treatment of aphthous ulcers in adults and adolescents 12 years of age and older. TRADENAME is not indicated for use in children below age 12 or in patients with an abnormal immune system.

We completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert, immediate container and carton labels). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved NDA 21-727.**" Approval of this submission by FDA is not required before the labeling is used.

If you choose to use a proprietary name for this product, the name and its use in the labels must conform to the specifications under 21 CFR 201.10 and 201.15. We recommend that you submit any proprietary name to the Agency for our review prior to its implementation.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and

effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have fulfilled the pediatric study requirement for this application.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to the Division of Dermatologic and Dental Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising,
and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Jacquelyn Smith., Regulatory Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Jonathan K. Wilkin, M.D.
Director
Division of Dermatologic & Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Stanka Kukich
9/29/04 09:40:51 AM
Sign off for Dr. Wilkin, Division Director

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

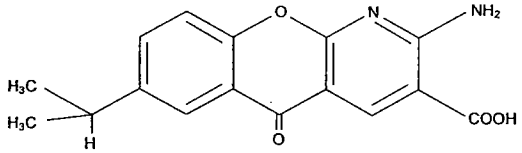
NDA 21-727

Approved Labeling

TRADENAME
(amlexanox) Mucoadhesive Patch, 2 mg
For Oral Cavity Use Only

Description: TRADENAME is a mucoadhesive patch that contains 2 mg of amlexanox per patch.

Amlexanox is 2-amino-7-isopropyl-5-oxo-5H-[1]benzopyrano [2,3-b]pyridine-3-carboxylic acid. It has a molecular formula of $C_{16}H_{14}N_2O_4$ and has a molecular weight of 298.30. Amlexanox is an odorless, white to yellowish-white crystalline powder. The structural formula is:



Each patch contains 2 mg of amlexanox as part of a multi-layer patch consisting of ethylcellulose, FD&C Blue #1, FD&C Red #40, hydroxyethylcellulose, hypromellose, methylparaben, modified starch, polycarbophil, povidone, propylene glycol, propylene glycol monostearate, purified water, sodium benzoate, sodium carboxymethylcellulose.

Clinical Pharmacology: The mechanism of action by which amlexanox accelerates healing of aphthous ulcers is unknown. *In vitro* studies have demonstrated amlexanox to be a potent inhibitor of the formation and/or release of inflammatory mediators (histamine and leukotrienes) from mast cells, neutrophils, and mononuclear cells.

Pharmacokinetics and Metabolism: After oral application of TRADENAME patches, the average maximum serum levels are 45.4 ng/ml (N=14), and 168 ng/ml (N=3) after application of one or three patches, respectively. The mean total exposure, AUC_{0-24}, is 258 ng•hr/ml, and 605 ng•hr/ml after application of one, or three patches, respectively.

After 3 full days of oral application of TRADENAME, four times a day, and one dose on Day 4, maximum serum levels ranged from BLQ (Below limit of quantification: 5 ng/mL in serum) to 79 ng/ml (N=24) prior to the first dose on Day 4, and also, had a similar range in the serum samples collected 2 hours post-dose. For application of two TRADENAME patches, the pre- and post-dose levels were BLQ to 164 ng/mL and BLQ to 117 ng/mL, (N=5) respectively. Post-dose levels are similar to or slightly higher than pre-dose levels, with the mean level of 9.8 and 16 ng/mL, respectively, for one TRADENAME patch and 44 and 44 ng/mL, respectively, for two TRADENAME patches.

CLINCIAL STUDIES

Study A

The efficacy of TRADENAME was established in one controlled clinical study, Study A, in which patients with one, two or three aphthous ulcers applied the patch(s) four times daily for 7 days. The study evaluated 303 patients receiving TRADENAME, 301 patients receiving the vehicle patch, and 97 patients receiving no treatment. Tobacco users and diabetics were excluded from clinical testing.

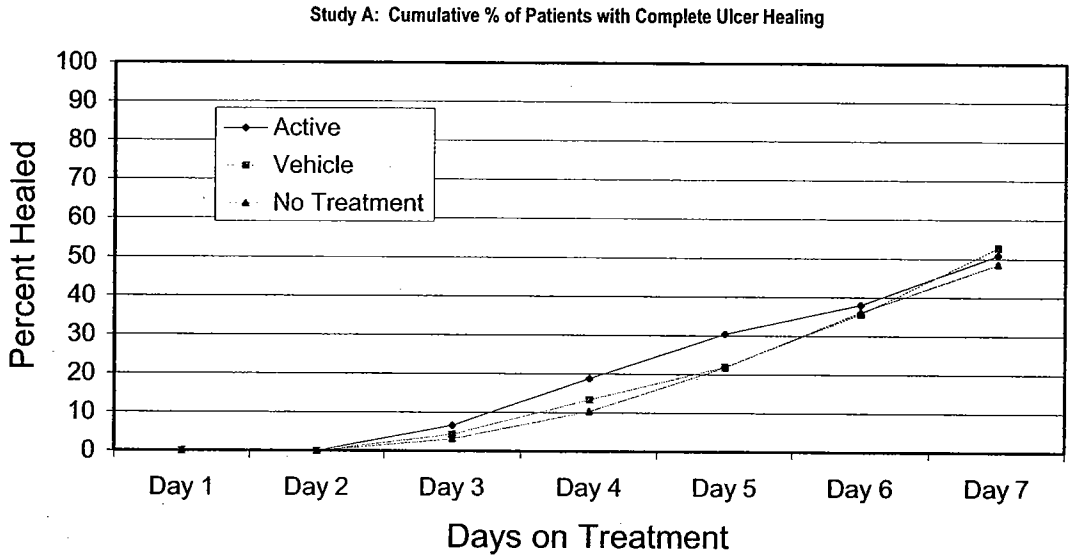
The endpoint agreed upon *a priori* was complete healing on Day 5. After 4 days of treatment (Day 5) there was a significant difference in percentage of patients with complete healing of ulcers (30.4% in the active group vs. 21.9% in the vehicle group). In the following table, the percentage of patients healed in each group at each day of the study is provided.

Number (%) of Patients with Complete Ulcer Healing Over Time – Study A

Time	Amlexanox (n = 303)	Vehicle (n = 301)	No-treatment (n = 97)
Day 3	20 (6.6%)	13 (4.3%)	3 (3.1%)
Day 4	57 (18.8%)	40 (13.3%)	10 (10.3%)
Day 5*	92 (30.4%)	66 (21.9%)	21 (21.6%)
Day 6	115 (38.0%)	107 (35.6%)	35 (36.1%)
Day 7	154 (50.8%)	159 (52.8%)	47 (48.5%)

*The comparison (p-value) of amlexanox vs. vehicle is statistically significant ($p<0.05$) at Day 5 only.

The data from the above table is provided graphically as follows:



Pain relief occurred in conjunction with healing of the ulcers. TRADENAME, by itself was not shown to be an analgesic medication.

Indications and Usage: TRADENAME is indicated for the treatment of aphthous ulcers in adults and adolescents 12 years of age and older. TRADENAME is not indicated for use in children below age 12 or in patients with an abnormal immune system.

Contraindications: TRADENAME, is contra-indicated in patients with known hypersensitivity to amlexanox or other ingredients in the formulation.

Precautions:
General

Wash hands immediately after applying TRADENAME directly to the ulcers with the fingertips. In the event that a rash or contact dermatitis occurs, discontinue use.

Use of TRADENAME in Smokers
Tobacco users may respond differently to TRADENAME. Smokers are known to have a lower incidence of aphthous ulcers than the general population, but were excluded from the clinical trials. Therefore, the effect of TRADENAME on smokers is not known.

Risk of Aspiration

There were no reports of accidental aspiration or detrimental swallowing of the patches in patients 12 and older during clinical trials. Nevertheless, it is recommended to apply TRADENAME at least 80 minutes prior to bedtime to avoid the possibility of aspiration of soft food-like particles that may come loose during erosion of the patch in the mouth. Keep out of the reach of children below the age of 12.

Carcinogenesis, Mutagenesis, Impairment of Fertility: Amlexanox was not carcinogenic when administered to mice for 18 months at dosages up to 100 mg/kg/day (approximately 12 times the maximum human dose when comparing on the basis of body surface area estimates) or to rats for 24 months at dosages up to 250 mg/kg/day (approximately 60 times the maximum human dose). Amlexanox was negative in bacterial mutation assays in Salmonella, E. coli, and B. subtilis, in a mouse lymphoma assay, and in a micronucleus assay conducted in mice.

Amlexanox did not affect reproductive performance (fertility) or ability of rats to deliver and rear pups (perinatal development) when administered at dosages up to 300 mg/kg/day (approximately 70 times the maximum human dose).

Pregnancy Category B:
Reproduction studies have been performed in rats and rabbits at doses up to 300 mg/kg/day (approximately 70 and 145 times the maximum human dose in rats and rabbits, respectively, when comparing on the basis of body surface area estimates) and have revealed no evidence of impaired fertility or harm to the fetus due to amlexanox. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: Amlexanox was found in the milk of lactating rats; therefore, caution should be exercised in administering TRADENAME to a nursing woman.

Pediatric Use: The safety of TRADENAME in pediatric patients between ages 12 and 17 was established in a study in which patients with aphthous ulcers (98 of whom were pediatric) applied the patch four times daily for 7 days with no significant topical or systemic adverse effects. In a separate, long-term study 106 patients with aphthous ulcers (30 of whom were pediatric) applied the patch four times daily for 28 days with no significant topical or systemic adverse effects. Use of TRADENAME in patients under 12 is not recommended due to the risk of aspiration.

Geriatric Use: Safety and effectiveness of TRADENAME in geriatric patients have not been established.

Adverse Reactions: In the combined safety database, no single adverse reaction was reported by more than 10% of patients. Adverse reactions reported by 9.8% of patients were pain or burning,

restricted to the site of application, occurring at the time of application. Adverse reactions reported by less than 2% of patients were irritation and paresthesia at the site of application.

Systemic adverse events that occurred during clinical trials, that were reported by less than 2% of patients, included headache, sore throat, and nausea. Mouth ulceration (new aphthous ulcers) was also reported at a rate of less than 2%.

The safety of TRADENAME was established in a long-term study in which 106 patients with aphthous ulcers applied the patch four times daily for 28 days with no significant topical or systemic adverse effects.

The following table provides a comparison of the adverse events reported by patients in the clinical trials who received TRADENAME, a vehicle patch, and no treatment.

Percentage of Patients with Adverse Events with an Incidence of > 1% - from All Clinical Trials

	Amlexanox	Vehicle	No treatment
Application Site Reactions	N = 409	N = 301	N = 97
Pain	29 (7.1)	25 (8.3)	NA
Burning	11 (2.7)	9 (3.0)	NA
Irritation	6 (1.5)	6 (2.0)	NA
Reaction NOS	5 (1.2)	0 (0)	NA
Paresthesia	3 (0.7)	4 (1.3)	NA
Gastrointestinal Disorders			
Mouth Ulceration (i.e., new aphthous ulcers)	5 (1.2)	13 (4.3)	6 (6.2)
Nausea	4 (1.0)	5 (1.7)	0
Sore Throat NOS	1 (0.2)	3 (1.0)	1 (1.0)
Investigations			
Liver function tests NOS abnormal	2 (2.0)	Not done	Not done
Nervous System Disorders			
Headache NOS	6 (1.5)	4 (1.3)	0

Overdosage: There are no clinical reports of overdosage. Gastrointestinal upset such as nausea, vomiting, and diarrhea could result from an overdose.

Dosage and Administration: TRADENAME should be applied as soon as possible after noticing the symptoms of an aphthous ulcer and should be used four times daily, preferably following oral hygiene after breakfast, lunch, dinner, and 80 minutes before bedtime. Up to three patches may be used at one time. Apply one TRADENAME patch to each ulcer. Use of the medication should be continued until the ulcer heals but no longer than 10 days. If significant healing or pain reduction has not occurred in 10 days, consult your dentist or physician.

Information for Patients:

1. Apply TRADENAME as soon as possible after noticing the symptoms of an aphthous ulcer. Wash hands before applying TRADENAME. Continue to use TRADENAME four times daily, preferably following oral hygiene after breakfast, lunch, dinner, and 80 minutes before bedtime. In all cases, ensure that the patch is firmly attached to the ulcer.

2. In case of multiple ulcers, apply one TRADENAME patch to each ulcer. Up to 3 patches may be used at one time.
3. Using clean dry hands, place the light colored side of the patch against the ulcer in the mouth and press gently. The patch will stick to the ulcer in the mouth and remain in place. In rare circumstances, patients may find that the patch does not adhere readily. In such cases reapply the patch and press gently for several seconds before removing the finger.
4. Wash hands immediately after applying TRADENAME.
5. Patients should not apply a patch within 80 minutes before bedtime, to ensure it has eroded before sleep.
6. Patients should avoid eating or drinking for an hour after applying the patch.
7. Following application, the patch will slowly erode in the mouth, generally disappearing entirely in 20-80 minutes. Depending on the location of the patch in the mouth, and factors such as the amount of saliva flow and mechanical action of the mouth, complete disappearance of the patch may take more or less time. Patients may feel small particles in the mouth as the patch erodes. These particles may safely be swallowed.
8. Use TRADENAME until the ulcer heals. If significant healing and pain reduction has not occurred in 10 days, consult your dentist or physician.
9. Keep out of the reach of children below age 12.

How Supplied: TRADENAME is supplied in bottles of 20 patches. NDC 67404-300-20

TRADENAME should be stored at 25 ^{0}C (77 ^{0}F)
[Caution: Avoid prolonged exposure to temperatures above 30^{0}C (86 ^{0}F)

RX ONLY

Manufactured for:
Access Pharmaceuticals, Inc.
Dallas, TX 75207

TRADENAME is a trademark of Access Pharmaceuticals, Inc.
August 2004

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-727

Medical Review(s)

Multi-Disciplinary Summary
NDA 21-727 TRADENAME (amlexanox 2 mg mucoadhesive oral patch)

Treatment of [ ] of aphthous ulcers in adults and adolescents 12 years of age and older

September 23, 2004

This new NDA for TRADENAME (amlexanox 2 mg mucoadhesive oral patch) for the treatment of [ ] of aphthous ulcers in adults and adolescents 12 years of age and older is recommended for approval by the review team.

CMC:

Recommendations by the CMC reviewer were limited to minor, but helpful, labeling issues. In particular, the stability data submitted by the sponsor did not support the storage conditions, which had to be revised in the label.

Pharm/Tox:

The submission contained no new nonclinical data, and referenced NDA 20-511 for Aphthasol®, the approved amlexanox 5% paste formulation approved in 1996. The reviewer recommended Pregnancy Category B. The reviewer further concluded that no toxicity relevant to the proposed clinical use was observed, and there are no nonclinical safety issues relevant to clinical use.

Biopharmaceutics:

The Pharmacokinetics of this product were assessed in a Phase 1 single-dose study, a Phase 3 multi-dose study and a Phase 1 study that evaluated the effects of amlexanox on the cytochrome P450 system. In addition, clinical safety data is available from the Aphthasol® paste formulation and the oral tablet formulation that is approved in Japan.

Amlexanox is absorbed largely through the GI tract. It was determined that absorption through the ulcer was insignificant. Amlexanox has a half-life of 3-6 hours and only 17% is eliminated through the kidney. There a no significant concerns in using this product in people with hepatic or renal limitations.

TRADENAME was demonstrated to have a relatively minor effect on various CYP450 isozymes (< 10 % inhibition or stimulation), and is therefore unlikely to have a significant effect on drugs and xenobiotics metabolized through the CYP450 pathway.

Clinical Safety:

Adverse events observed in clinical trials with this product were infrequent and non-serious.

Clinical Efficacy and Biostatistics:

This reviewer agrees with Dr. Hyman's clinical review on all points. However a clarification needs to be made about the extent to which approval is based on findings from studies using the early formulation. While Dr. Hyman has not specifically referred to the data from the early formulation as "supportive," he does refer to that data at various points in his review. In particular, his discussion of the non-inferiority comparison between vehicle and no treatment refers to data from the Phase 3 trial using the early formulation. He also refers to the data from the same trial in his discussion of efficacy in adolescents age 12 – 17. For the record, the Division has concluded that the two formulations are different enough that they cannot be considered "the same" absent a bioequivalence study to demonstrate that they are the same. No study has been conducted; therefore the data from the studies of the early formulation cannot be used to support the Agency's finding of efficacy for this product.

The Division views this product as a line extension of the approved product Aphthasol® (amlexanox oral paste), 5 mg, and consequently agreed to accept a single study to support efficacy. The agreed upon criteria for success were that the active had to be statistically significantly superior to the vehicle and the vehicle had to be non-inferior to no treatment. The pre-specified non-inferiority margin was -8%. These criteria for success were based on FDA's draft guidance document, *Chronic Cutaneous Ulcer and Burn Wounds – Developing Products for Treatment.* As was discussed in both Dr. Hyman's clinical review and in the Biostatistics review, the non-inferiority comparison between vehicle and no treatment (-9.2%) was close, but fell slightly outside the pre-specified non-inferiority margin (-8%). However, it should be noted that the point estimates for the vehicle and no treatment arms were very close (21.9% for vehicle v. 21.6% for no treatment), which supports the fact that the vehicle is not deleterious. In addition, the small number of patients in the no treatment group make it difficult to show a difference between groups.

This reviewer feels that the failure to meet this criterion should not result in failure to approve this product. I recommend approval for this NDA.

Recommendation:

In summary, all disciplines have recommended that this new dosage form for amlexanox be approved. The sponsor has agreed to the labeling attached to Dr. Hyman's clinical review.

John V. Kelsey, DDS, MBA
Lead Dental Officer

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/s/

John Kelsey
9/24/04 04:10:14 PM
MEDICAL OFFICER

Jonathan Wilkin
9/24/04 04:39:23 PM
MEDICAL OFFICER
I concur with the Dental TL that there is no need for reliance on data regarding the earlier patch formulation, and that there is sufficient information provided that the vehicle is not deleterious.

CLINICAL REVIEW

Application Type	NDA
Submission Number	21-727
Submission Code	N-000
Letter Date	December 4, 2003
Stamp Date	December 9, 2003
PDUFA Goal Date	October 9, 2004
Reviewer Name	Frederick Hyman, DDS MPH
Review Completion Date	August 26, 2004
Established Name	Amlexanox
(Proposed) Trade Name	OraDisc™A
Therapeutic Class	Anti-inflammatory
Applicant	Access Pharmaceuticals, Inc.
Priority Designation	S
Formulation	Adhesive Oral Patch
Dosing Regimen	One Patch q.i.d.
Indication	Treatment of[redacted] Aphthous Ulcers in Adults and Adolescents 12 Years of Age and Older
Intended Population	Adults and Adolescents 12 Years of Age and Older

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

OraDiscA patch (2 mg amlexanox in a mucoadhesive patch) has shown adequate evidence of efficacy in the healing of aphthous ulcers. In one placebo-controlled, randomized and blinded clinical trial of seven days duration, a significantly higher percentage of aphthous ulcer patients experienced complete healing after four days of OraDiscA treatment compared to those who received a vehicle disk. Data from one additional non-pivotal phase 3 trial was also used to clarify two of the efficacy outcomes from the pivotal trial. OraDiscA has been shown to be safe for its intended use as recommended in the labeling by all means reasonably applicable to the assessment of safety. These include comparison of adverse events between groups in the clinical trials, reviewing laboratory data, reviewing postmarketing reports from already marketed amlexanox products, and gathering chronic use data from an open label safety trial. Demographic data allowed evaluation of safety and efficacy in subgroups based upon race, gender and age. Sufficient data have been submitted and reviewed to provide adequate directions for use, including data that describe a safe and effective dose. This new drug application is recommended for approval.

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

No postmarketing risk management activities are being recommended.

1.2.2 Required Phase 4 Commitments

No Phase 4 clinical study commitments have been proposed.

1.2.3 Other Phase 4 Requests

There are no other Phase 4 requests for the sponsor.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

OraDisc™A is the proposed trade name for an adhesive disk containing 2% amlexanox. Access Pharmaceuticals seeks approval of OraDiscA for the treatment of aphthous ulcers when applied topically to the ulcer site. The recommended duration of use is seven days for each aphthous ulcer occurrence. Amlexanox is not a new molecular entity, having been approved for the same indication in December 1996 as the active ingredient in Aphthasol®, an oral paste containing 5% amlexanox.

The clinical testing which formed the basis for evaluating safety and efficacy of OraDiscA consisted of three Phase 1 studies, one Phase 2 study, two Phase 3 trials and an open label safety study, for a total of 592 subjects assigned to either OraDisc, a vehicle patch, or no treatment. Of this total, 493 were exposed to amlexanox for seven days, and 99 were exposed to amlexanox for 28 consecutive days. Every subject who was exposed to OraDiscA in any of the clinical trials was included in the safety analysis, whereas the efficacy evaluation was based upon one pivotal phase 3 trial.

In addition to the above mentioned studies, the sponsor also relied upon data from marketed amlexanox products for additional safety support; these include not only Aphthasol as mentioned above, but also 50-mg amlexanox oral tablets that are approved in Japan for internal use as an agent to treat asthma and allergic rhinitis. Most of the pharmacology data and much of the biopharmaceutics data was gathered from the study of Aphthasol and resubmitted to this NDA. Postmarketing data from Aphthasol and the oral tablets were also submitted to this NDA in support of amlexanox safety.

1.3.2 Efficacy

Two phase 3 trials were conducted and submitted to this NDA. One of the phase 3 trials is considered pivotal for efficacy and the other phase 3 trial is not. The trials had identical efficacy endpoints, statistical analyses and evaluations; the non-pivotal phase 3 trial is not considered pivotal because it was conducted with an earlier formulation of OraDisc. The earlier formulation differed in the composition of the backing material from the final, to-be-marketed formulation of OraDiscA that was used in the pivotal trial.

The primary outcome variable for the efficacy trials is the percentage of subjects who had healed (defined *a priori* as all ulcers reaching the size of 0 mm) after four days of treatment. To achieve approval, it was specified that there be a statistically significant improvement of the percentage healed in the OraDiscA group compared to the vehicle group. In addition, the agreement between the sponsor and the Agency was that the percentage of subjects healed after four days on the vehicle treatment would be statistically non-inferior to the no-treatment group results. There are three secondary endpoints, which include 1) the number of days until healing 2) the percentage of patients with pain resolution after four days of treatment and 3) the number of days until pain resolution.

The study design was adequate with minimal opportunity for bias, and had adequate control groups, consisting of both a vehicle group and a no-treatment group. The trials were also sufficiently well-designed to allow the assessment of benefit; they were of adequate duration, employed appropriate entry criteria, tested an appropriate dose, and employed sound statistical analyses. Furthermore, the trial was successful in recruiting subjects of both genders, all age groups over 12 years, and all major U.S. racial groups.

Two problems arose during the review process which do not prevent approval, but did require additional evaluation. One flaw in the pivotal trial design is that it was underpowered for the non-inferiority comparison as pre-specified, due to an inaccurate

estimate of the expected results. The borderline demonstration of non-inferiority as set forth in statistical testing necessitated consideration of the stronger results in the non-pivotal trial. Another review difficulty was the interpretation of the secondary variables that examined pain relief. Whereas the efficacy results of the comparison between OraDiscA and the no treatment group demonstrated that OraDiscA contributes significantly to pain relief, the comparison of OraDiscA to vehicle disk does not reach statistical significance for pain relief. The pain relief that subjects experienced resulted from a combination of an increase in the percentage of subjects healed on Day 5 as well as the protective effect of OraDiscA to the ulcer site. The labeling should therefore reflect that subjects can expect pain relief in addition to healing while using OraDisc, but that amlexanox is not an analgesic.

The sponsor has adequately demonstrated that OraDiscA effectively increases the percentage of patients with aphthous ulcers who are healed at Day 5 compared to those who received a vehicle disk. They have also shown that the effect is valid, and was not caused by the vehicle exerting some detrimental effect on the aphthous ulcers. The effect was also valid in individuals with up to three concomitant ulcers.

OraDiscA will provide an additional therapy to the current armamentarium for treatment of aphthous ulcers. Current treatments include anti-inflammatory drugs, analgesic drugs, antimicrobial drugs and mucosal protectants. To date, the only drug that has been specifically approved to treat aphthous ulcers is Aphthasol, which is the 5% paste form of amlexanox. Although the results from OraDiscA appear similar to those of Aphthasol, no comparative testing was performed for efficacy, nor was comparative questioning on patient preference or ease of use evaluated.

1.3.3 Safety

A total of 592 subjects were exposed to OraDiscA in all studies. Of these, 493 completed studies in which they used OraDiscA for seven days and 99 subjects completed a long-term study in which they used OraDiscA for 28 days. The trials of seven days duration tested the drug for the recommended duration of application for each aphthous ulcer incident. Only the open-label safety study was long enough to simulate six months of use. Since most aphthous ulcer sufferers develop ulcers on a fairly regular basis, it is not unusual to be treated for a seven-day cycle 10-12 times per year.

Men and women, individuals of Caucasian, African American and Hispanic background, and adolescents from 12 – 17 were adequately represented. Patients who were excluded from the study such as diabetics and tobacco users do not limit the relevance of safety assessment, although their exclusion does leave concerns about generalizability of efficacy and will be addressed in the proposed labeling. There were no class effects evaluated, other than potential for local irritation from the topical drug products as a group.

There were no reports of death or other serious adverse events during any of the clinical trials. The most common adverse events reported were local irritation reactions such as

pain, irritation, and burning, which had incidences in the pooled safety studies of between 1% and 9%. Systemic events were mild and very few; they included nausea, sore throat, and headache. Since the incidence of these reactions is similar in the OraDiscA groups to the vehicle group, it is likely that the reported local events result from the physical presence of the disk more than from the amlexanox itself. There appears to be no significant potential for abuse or overdosage, or negative impact on growth or development. Because of the lack of data, it has been placed in pregnancy category B, with use during pregnancy and lactation recommend only if the benefit outweighs the risk.

Data gathered was adequate to assess safety, and included not only adverse event monitoring during the trials, but also pre-marketing and postmarketing evaluations for Aphthasol and postmarketing data that was available for oral amlexanox. Laboratory parameters were monitored during the open label study at baseline and during the final visit. Although there was no control group for comparison, the subjects were compared to their baseline values. There were very few shifts in lab values, and for those few, no cause for concern for patient safety was identified. Vital signs and ECG data were not collected during the clinical trials, but there was no reason to require this for a topical drug with a safe history.

One limitation of the data is that only 99 subjects were evaluated for chronic use of this drug - this is lower than the numbers suggested by the current ICH guidance on extent and duration of exposure needed to assess long-term safety. This smaller than ideal number is balanced against the very positive safety profile gathered from the long-term safety study as well as the profile from the approximately 500 subjects on Amlexanox in the normal seven-day cycle. In addition to that, the sponsor has submitted safety data from Aphthasol, which contains the same amount of amlexanox as OraDiscA and is approved for chronic use.

The safety profile of OraDiscA is comparable to Aphthasol, the other currently approved treatment available for aphthous ulcers in the U.S.

1.3.4 Dosing Regimen and Administration

The appropriate dosing regimen is one OraDiscA patch applied directly to the aphthous ulcer four times per day until the ulcer heals. This was the only dosing regimen tested in the clinical trials and is the same dosing as the approved amlexanox product, Aphthasol.

1.3.5 Drug-Drug Interactions

No drug-drug interactions have been identified.

1.3.6 Special Populations

OraDiscA was tested in children between the ages of 12 and 17. Although the safety data were adequate to conclude that it is safe for use in children of this age, the sample size was too small in this age group to be conclusive about the efficacy data in children.

However, due to the lack of literature to suggest that aphthous ulcers in adolescents behave differently than in adults, the Agency believes that efficacy can be extrapolated from the adult data. The pediatric section of the label will be written to reflect the trial results for pediatric patients.

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2 INTRODUCTION AND BACKGROUND

Aphthous ulcers are small, round to ovoid lesions, generally less than five millimeters in diameter, which are found mainly on the non-keratinized, mobile mucosa of the lips, cheeks, floor of the mouth, and tongue. The ulcers are flat, are covered with a gray-white pseudomembrane of fibrin and other debris, and are surrounded by a raised erythematous rim. They can be divided into three classes:

- Minor aphthae: Single minor (less than 10 mm) lesions are by far the most common presentation. Such lesions heal in one to two weeks. Some patients have multiple minor lesions. Although individual lesions heal in one to two weeks, new lesions may appear as the old ones are healing.
- Major aphthae: Major aphthae are lesions of over 10 mm in diameter and may occur in any area of the mouth. They last up to six weeks and, unlike minor aphthae, heal with scarring.
- Herpetiform ulcers: The least common form of aphthous ulcers is herpetiform ulcers, which occur as multiple small clusters of pinpoint ulcers. Although the lesions are herpes-like in appearance, herpes simplex virus cannot be cultured from them.

Unless otherwise noted in the remainder of this review, all references to aphthous ulcers means "minor aphthae." Although exact numbers vary depending upon the source, aphthous ulcers are a common phenomenon with an incidence of approximately 50% in the general population. Most literature reports that approximately 50% of men have reported a history of aphthous ulcers as have 57% of women. A survey conducted by the National Institutes of Dental and Craniofacial Research cites the number of school-age children reporting a history of recurrent aphthous ulcers as 37%. A genetic predisposition to this condition, which occurs in otherwise healthy people, has been demonstrated through population studies and twin studies.

In addition to appearing in healthy individuals, aphthous ulcers also appear in some diseases, notably AIDS, Behçet's syndrome, and inflammatory bowel disease, and in some deficiency states, such as iron or folate deficiency. Tobacco users have been reported to be less likely to develop aphthous ulcers than is the general population (Grady, Ernster, Stillman, and Greenspan, 1992).

Aphthous ulcers are thought to be formed through a T cell attack on some unidentified epidermal antigen. The triggering event for the T cell attack is not known. A number of attempts have been made to detect the presence in the ulcer of viruses or of aberrant, intracellular forms of bacteria that might be the source of antigen triggering the attack. The results of these studies have been almost uniformly negative, although such a source of antigen cannot be completely ruled out.

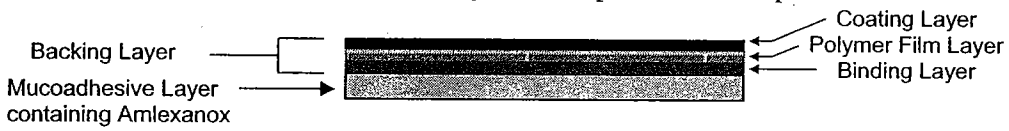
Trauma is known to cause aphthous ulcer formation in individuals who are predisposed to them. It is believed that if simple trauma can initiate an aphthous ulcer in susceptible

individuals, some imbalance in the immune system must allow the ulcer to occur, instead of the normal sequence of inflammation and healing. Several differences have been found between aphthous ulcers and "ulcers" induced by trauma in normal individuals. Compared to traumatic ulcers, aphthous ulcers contain three and a half times more TNF alpha-containing cells; more adhesion molecules; 60% more mast cells; 50% more XIIIa+ cells; and seven times more gamma/delta T cells.

2.1 Product Information

OraDisc™A is the proposed trade name for a mucoadhesive disk containing 2% amlexanox. Access Pharmaceuticals seeks approval of OraDiscA for treatment of aphthous ulcers when applied topically to the ulcer site. Amlexanox is not a new molecular entity, having been approved as the active ingredient in Aphthasol®, an oral paste containing 5% amlexanox. Aphthasol was approved on December 17, 1996 as NDA 20-511 for the treatment of signs and symptoms of aphthous ulcers in immunocompetent individuals. The dosage for Aphthasol paste is ¼ inch of paste (containing 2 mg of amlexanox) applied four times per day to the ulcer site. The proposed dosage for OraDiscA is one patch (containing 2 mg of amlexanox) applied four times per day to the ulcer site. Although the dosage of active ingredient is identical, a new delivery system necessitates a new NDA.

OraDiscA is an adhesive wafer of ½" diameter with very little thickness (275 μm). One side of the disk contains a 3-layered cellulose backing. The other side of the disk contains amlexanox in a mucoadhesive layer that is placed on the aphthous ulcer.



Amlexanox is 2-amino-7-isopropyl-5-oxo-1H-(l)benzopyrano-(2,3-b)pyridine-3-carboxylic acid. It has been shown to have anti-allergic activity, to inhibit bronchoconstriction, and to have some anti-inflammatory effects in models for both chronic and acute inflammation. Although the sponsor has stated in this submission that the exact mechanism of action in healing aphthous ulcers is not known, both *in vivo* and *in vitro* studies of the mechanism of action of amlexanox have indicated that the agent has the following mechanisms of action:

- Inhibition of the immunologically-stimulated release of histamine from mast cells.
- Inhibition of leukotriene D_4 generation.

The applicant's proposed indication is "OraDisc ™A (Amlexanox 2 mg, Mucoadhesive Patch) is indicated for the treatment of [ ]aphthous ulcers in adults and adolescents 12 years of age and older."

The 2-mg patch of amlexanox is the only dose of OraDiscA proposed, and the dosing regimen is one patch placed on the area affected by the aphthous ulcer four times per day. Although most individuals only experience one aphthous ulcer at a time, for those who experience multiple concurrent aphthous ulcers, the drug is proposed to be used to treat up to three ulcers at one time.

2.2 Currently Available Treatment for Indications

The treatments used for aphthous ulcers can be divided into four categories: Anti-inflammatory drugs, analgesic drugs, antimicrobials drugs, and mucosal protectants.

Anti-inflammatory drugs

- Corticosteroids: Steroids are a standard treatment for many types of inflammation. They are mainly used topically for aphthous ulcers, but in severe cases, oral steroids are sometimes given short-term. Steroids, however, even when used topically, have side effects that limit indiscriminate use.
- Thalidomide: Treatment of Aphthous ulcers is not a labeled indication for thalidomide. However, it is used to treat long-standing serious major aphthous ulcers, mainly in AIDS patients. This drug has serious toxic effects, neuropathy in particular, and is a strong teratogen.
- Amlexanox: Amlexanox is applied topically, currently available as Aphthasol 5% amlexanox paste.

Analgesic drugs

- Local anesthetics: Local anesthetics are the ingredients used in over-the-counter drugs for aphthous ulcers. They must be applied repeatedly for continuous pain relief.
- Acetaminophen and NSAIDs are sometimes used systemically for the relief of aphthous ulcer pain.

Antimicrobial drugs

- Chlorhexidine rinses are labeled for treatment of gingivitis, but are sometimes prescribed off-label as an aid in reducing bacteria in the mouth with the hopes of reducing severity of aphthous ulcers. It has not been scientifically demonstrated to be effective for aphthous ulcer treatment or prevention.
- Tetracycline is used topically as a rinse or paste, also an off-label use. Although not validated, its action on aphthous ulcers is thought to be due to its inhibition of metalloproteinases.

Mucosal Protectants

- Carboxycellulose is an acrylic covering used after dental procedures to cover abrasions and incisions. It is sometimes used to coat aphthous ulcers.

2.3 Availability of Proposed Active Ingredient in the United States

Amlexanox is marketed in the US as a 5% oral paste formulation in Aphthasol®, which was approved by the U.S. Food and Drug Administration for the treatment of aphthous ulcers in 1996. Section 2.1 of this review supplies a brief description of the labeling and dosing of Aphthasol. In the United States, there have been no major safety concerns or labeling changes for Aphthasol. Because Aphthasol was approved in the Division of Dermatologic and Dental Drug Products, the Division is familiar with the product. There were no serious safety issues during the approval process for Aphthasol, and the knowledge of its safety profile has been very helpful in the drug development of OraDiscA to both the sponsor in gathering safety data and the Agency for evaluating it. In terms of efficacy, the determination of clinical benefit of the observed treatment was discussed in depth. From those past deliberations, both the Agency and the Sponsor were better aware of selecting outcome variables that presented the most realistic evaluation of the drug's effect and how to report it for easiest interpretation and analysis.

2.4 Important Issues With Pharmacologically Related Products

Amlexanox is an anti-inflammatory drug which inhibits leukotriene and histamine. In order to compare amlexanox to similar products, it is first necessary to note that amlexanox, as well as pharmacologically-related products, have a history in the world marketplace for systemic use. It would be expected that OraDiscA's 2 mg of amlexanox per dose - acting topically until disintegrated and being ingested - would exert very little systemic effect compared to ingestion of 50 mg per dose. Nonetheless, systemic absorption is valuable background information in evaluating adverse events that emerge in OraDiscA's trials, and is useful to note should a future safety signal arise. Therefore, for completeness, these pharmacologically related products that are used internally will be examined. Following that discussion, the remainder of this section will examine relevant issues with two related groups of drugs: 1) topical products, and 2) drugs delivered through an oral patch.

Amlexanox is available in Japan as an oral tablet containing either 25 mg or 50 mg of active ingredient, where Takeda Pharmaceuticals markets it for the treatment of bronchial asthma (approved in 1987) and allergic rhinitis (approved in 1989). Takeda Pharmaceuticals also produces amlexanox in a nasal solution of 0.25%, which is marketed in Japan for the treatment of allergic rhinitis (approved in 1988). Senju Pharmaceuticals markets amlexanox in an ophthalmic solution of 0.25% in Japan for the treatment of allergic conjunctivitis (approved in 1989). There is very little literature about the mechanism of action or adverse events profile associated with the Japanese use of amlexanox when taken internally. However, Amlexanox very closely resembles another leukotriene inhibitor, sodium cromoglicate, which has been well-studied in terms of adverse events and toxicity. Sodium cromoglicate is not marketed in the United States, but is widely available in Europe. Martindale includes a detailed review of sodium cromoglicate, which is administered by mouth at a dose of 25 or 50 mg three

times daily for the management of asthma and allergic rhinitis. Most of these effects discussed here are therefore associated with an amlexanox-related drug taken internally at 10 – 20 times the dosage for OraDiscA.

Inhalation of sodium cromoglicate may cause transient bronchospasm, wheezing, cough, nasal congestion, and irritation of the throat. Nausea, headache, dizziness, an unpleasant taste, and joint pain and swelling have been reported. Other reactions, which have sometimes occurred after treatment for several weeks or months, include aggravation of existing asthma, urticaria, rashes, pulmonary infiltrates with eosinophilia, dysuria, and urinary frequency. Severe reactions such as marked bronchospasm, laryngeal edema, angioedema, and anaphylaxis have been reported rarely; these have sometimes been referred to as pseudo-allergic.

Intranasal use of sodium cromoglicate may cause transient irritation of the nasal mucosa, sneezing, and occasionally epistaxis. Nausea, skin rashes, and joint pain have occurred when it is taken by mouth. Transient burning and stinging have occasionally been reported following use of sodium cromoglicate eye drops.

The topical drug products, as a group, often share the common concern of local irritation. Therefore, a thorough examination of local irritation and sensitization was performed for OraDiscA, both through animal toxicology studies and evaluation of human experience. Results of oral, ophthalmic, and dermal irritation as well as sensitization studies revealed no safety concerns that warrant further testing. Refer to Section 3.2 (Animal Pharmacology/Toxicology) and Section 7.1.5 (Common Adverse Events) of this review for further detail on those studies.

Because of this product's unique delivery system as an oral adhesive patch, a drug with a very similar delivery system is noted here. Striant® Testosterone buccal system is a delivery system for testosterone that when applied to the buccal mucosa, slowly releases testosterone, allowing for absorption of testosterone through gum and cheek surfaces that are in contact with the buccal system. Since venous drainage from the mouth is to the superior vena cava, trans-buccal delivery of testosterone circumvents first-pass (hepatic) metabolism. The patches differ from OraDiscA, therefore, in that Striant is designed to remain intact for 12 hours, at which time it is removed and replaced with a new patch whereas OraDiscA is designed to dissolve into a paste within one – two hours, and ultimately be swallowed. Although OraDiscA does not achieve its action through systemic action, the Agency recognizes through the example of Striant how easily oral patches can be absorbed into the circulation. As a result, the amount of amlexanox absorbed via the buccal route versus through ingestion was examined through pharmacokinetics studies (Refer to Section 5 - Clinical Pharmacology). It is noteworthy that the most common adverse event associated with Striant is oral irritation at the site of placement with an incidence of approximately 10%. To ascertain that the potential for local irritation of OraDiscA could not negate the effects of amlexanox on healing, the sponsor designed the trial with a vehicle arm and a no treatment arm. One of the primary outcome variables is a comparison of vehicle to no treatment to demonstrate that the

OraDiscA vehicle is not detrimental to healing of the aphthous ulcer when compared to no treatment.

2.5 Presubmission Regulatory Activity

A pre-IND meeting was held on November 10, 1999 during which several general guidance questions were proposed by the sponsor and answered by the Agency . The IND for OraDiscA was opened on March 2, 2000 and assigned number 59,949. Comments were provided to the sponsor by the Agency about details of the proposed protocol, but there were no safety issues that prevented or delayed initiating trials under the IND. The sponsor's initial study plan included a proposed endpoint of complete pain resolution. The Agency suggested complete resolution of the ulcer as a better endpoint for the proposed indication and the sponsor concurred.

Just prior to conducting their pivotal trial, the sponsor made a decision regarding a formulation change that had major regulatory impact. There was an earlier formulation of the disk containing a [ ] backing that needed to be peeled from the disk prior to placement. The new, to be marketed, formulation eliminated the [ ] layer, and instead substituted a cellulose film that dissolves during use and therefore is not removed before disk placement. The early formulation had been used in Phase 1 and Phase 2 trials, including a trial that the sponsor called a "phase2/3 study." When the sponsor submitted the protocol for the Phase 2/3 study, they had been advised by the Division to request an EOP2 meeting before proceeding with any phase 3 trials. They had declined, stating that the Phase 2/3 trial was not intended to be pivotal.

When the sponsor requested and was granted an EOP 2 meeting, held on August 20, 2001, the final to-be-marketed formulation was proposed for use in the phase 3 pivotal trial. One of the questions that the sponsor asked of the Agency in the EOP2 meeting package was whether the already-completed Phase 2/3 trial could be regarded as pivotal. The Agency informed the sponsor that the new to-be-marketed formulation is sufficiently different from the old formulation that results from studies with the older formulation would not be considered pivotal towards approval. The Agency further stated that if the sponsor would only be submitting one pivotal trial with the new formulation, it would be expected to be "very persuasive with robust results and no significant flaws" to gain approval (exact quote from EOP2 meeting minutes).

Also during the EOP2 meeting, the Agency provided the sponsor with several clinical comments about their proposed Phase 3 pivotal study. As a result, the sponsor revised their Phase 3 protocol and submitted it as a 45-day special protocol assessment (SPA) on December 20, 2001. The Agency reviewed the SPA and gave comments, which the sponsor responded with a revised phase 3 protocol for concurrence. Based upon the comments made during the EOP2 meeting, and the comments provided during the SPA review and its follow-up, the following agreements were made between the sponsor and the Agency:

1. To fulfill the pediatric requirement, subjects would be enrolled between the ages of 12 and 17, with 25% of the subjects between the ages of 12 and 14.
2. To more adequately assess adverse events, the sponsor would ask specific questions, rather than rely on broad spontaneous reporting. They revised the protocol by adding two questions as follows: "Have you noticed any change in your health since the last visit?" and "Did you experience any pain or discomfort when using the patches?" They also queried the subjects about ease of application and whether the patch remained in place on a 0-10 scale. The sponsor also proposed a separate study of 18 subjects to measure the erosion of the patch and whether loose particles were common during use.
3. The sponsor originally proposed to treat and follow only one ulcer, even if more than one was present at the time of study enrollment, but changed the protocol to comply with the Agency's comment. The Agency had advised allowing for evaluating up to 3 concomitant ulcers should subjects present with them, to mimic the actual use conditions.
4. The Agency clarified that the "win" criterion would be that the percentage of aphthous ulcers that resolved with amlexanox disk would be statistically superior to the percentage of aphthous ulcers that resolved with vehicle disk. The second condition of win would be that the vehicle is not inferior to no treatment to which the sponsor agreed and proposed a 97.5% one-sided lower confidence interval of -8%.
5. The Agency offered to defer until Phase 4 demonstration of safety in 300-600 subjects on active for at least six months. The sponsor declined the offer and stated that they would submit 6-month safety data with the NDA.

At a guidance meeting held on August 13, 2003, shortly prior to filing the NDA, the sponsor asked for Agency concurrence that their Phase 3 study was very persuasive. The agency responded that on the surface, the results did not appear very persuasive, but that it would be a review issue should the sponsor file the NDA. The Agency suggested a [ ] With a successful outcome, the results of studies with the old formulation could be considered towards NDA approval. The sponsor proposed [ ] The sponsor planned [ ]

After discussion during an internal midcycle review meeting held on May 25, 2004, it was decided that one successful pivotal study that could demonstrate safety and efficacy of the drug would be sufficient. This was based upon the decision that this new drug was a new delivery system of an already marketed drug containing the already approved dose. A relevant CDER Guidance for Industry entitled, *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, Section II.C.2a.: "Different doses, regimens, or dosage forms" was cited and states the following:

"It may be possible to conclude that a new dose, regimen, or dosage form is effective on the basis of pharmacokinetic data without an additional clinical efficacy trial where blood levels and exposure are not very different or, even if quite different, there is a well-understood relationship between blood concentration and response. Where the relationship between blood concentration and response is not so well understood and the pharmacokinetics of the new dose regimen, or dosage form differ from the previous one, clinical efficacy data will likely be necessary to support effectiveness or a new regimen. In this case, a single additional efficacy study should ordinarily be sufficient."

Since the effect of the drug is topical, pharmacokinetic data alone is not sufficient to assess the local effect. Because both the OraDiscA form of amlexanox and Aphthasol paste are labeled to deliver 2 mg of amlexanox to the aphthous ulcer four times per day, OraDiscA is appropriate for regulation under this guidance document. The Agency decided that one pivotal trial would be sufficient with standard criteria for persuasiveness. The sponsor was informed by t-con of May 28, 2004 that, after extensive discussion, it had been decided that the additional studies would not be required and that the Agency could complete its review without them.

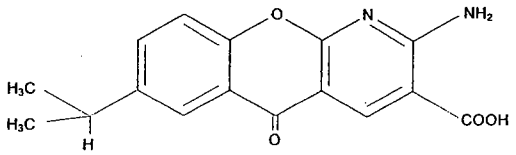
2.6 Other Relevant Background Information

In section 2.4 of this review the approval of amlexanox tablets in Japan for treatment of allergic rhinitis, allergic conjunctivitis, and for asthma has been discussed. The adverse events profile of amlexanox as used for these indications is discussed in section 7.1.17. It has also been pointed out in both of those sections that the dose of amlexanox as taken internally is approximately 20 times the dose that is delivered in the OraDiscA. Information from this foreign marketing does not raise concerns about the approval of OraDiscA.

3 Significant Findings from Other Review Disciplines

3.1 CMC (and Product Microbiology, if Applicable)

OraDisc™A is a mucoadhesive patch that contains 2 mg of amlexanox as part of a multi-layer patch consisting of ethylcellulose, FD&C Blue #1, FD&C Red #40, hydroxyethylcellulose, hypromellose, methylparaben, modified starch, polycarbophil, povidone, propylene glycol, propylene glycol monostearate, purified water, sodium benzoate, and sodium carboxymethylcellulose.
Chemical Name: 2-amino-7-isopropyl-5-oxo-5H-[1] benzopyrano [2, 3-b] pyridine-3-carboxylic acid.
Structural formula



Empirical Formula: $C_{16}H_{14}N_2O_4$
Molecular Weight: 298.30
Physicochemical Properties: Amlexanox is an odorless, white to yellowish-white crystalline powder insoluble in water.

The CMC reviewer has uncovered a problem with the sponsor's proposed labeling for drug stability. The analytical results identify a lack of 12-month stability at [redacted] although the proposed label recommends storage at up to that temperature. The data does however, support adequate stability at up to 25° C. The labeling will be modified to reflect the correct storage conditions.

3.2 Animal Pharmacology/Toxicology

Little potential for toxicity was observed in a battery of toxicology studies conducted with amlexanox that included acute, subchronic, chronic, carcinogenicity, genetic, and reproductive studies. No-effect-levels (NOELs) in these studies were substantial multiples of the proposed human exposure.

The submission contained no new nonclinical data. The application references NDA 20-511, the application for Aphthosol 5% amlexanox paste, approved by FDA in 1998. NDA 20-511 contains the following nonclinical studies: acute toxicology, repeat dose toxicology, genetic toxicology, carcinogenicity, reproductive toxicology, and special toxicology including nasal cavity irritation, nasal mucosal irritation and an ocular irritation study. The drug is recommended for pregnancy category B through review of reproduction studies which have been performed in rats and rabbits at doses up to 300 mg/kg/day (approximately 70 and 145 times the maximum human dose in rats and rabbits, respectively, when comparing on the basis of body surface area estimates). Those studies revealed no evidence of impaired fertility or harm to the fetus due to amlexanox. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

The pharmacology reviewer concluded that no toxicity relevant to the proposed clinical use was observed and there are no nonclinical safety issues relevant to clinical use.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The primary source of data used in this review is the clinical trials conducted by the sponsor, Access Pharmaceuticals. Additional safety support also relies on data from the submission of Aphthasol amlexanox 5% cream, which Access Pharmaceuticals owns. (Block Drug company, which originally owned and sponsored Aphthasol, sold the product to Access shortly after approval.) Postmarketing safety data from Japan has also been submitted for products containing amlexanox that are approved there in higher dosages for oral ingestion to treat allergic rhinitis, allergic conjunctivitis and asthma, as well as in eye drops.

One consultation was requested by this Division for clinical microbiology. A clinical microbiologist from the Division of Anti-infective Drug Products (HFD-520) in FDA's Center for Drug Evaluation and Research submitted a written review, which is summarized in the Clinical Microbiology section of this review (Section 6.1.5) No Advisory Committee has been convened to discuss any component of this NDA review. Literature searches were performed, including through PubMed and Micromedix databases primarily to provide further information on safety.

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4.2 Tables of Clinical Studies

	Study Title	Number of Subjects on Active	Number of Subjects on Vehicle	Number of Subjects on No Treatment	Safety Evalu-ations	Duration (Days)	Formulation (To-Be-Marketed) or Early
Phase 1 Clinical Trials							
AP-C-9E02	A Double-blind, Ramdomised, Vehicle-controlled, Parallel-group Study to Determine the Effects of Amlexanox Disc 2 mg in Preventing Recurrent Aphthous Ulcers in Patients Presenting at the Prodromal Stage	26	26	0	Day 4	4	Early
AP-C-9U05	A Phase I Study to Assess the Safety and Irritation Potential of OraDisc™A, 2 mg, and its Vehicle after Three 24-hour Occlusive Applications on the Skin of Healthy Volunteers	32	32	0		3	Early
Phase 2 and 3 and Open-Label Clinical Trials							
AP-C-1U106	A Phase 3 Evaluator-blinded, randomized, parallel-group Study to Determine the Effects of the Amlexanox 2 mg mucoadhesive Patch (OraDisc™A) on the Healing of Recurrent Minor Aphthous Ulcers as Compared with Vehicle Mucoadhesive Patches or No Treatment	303	301	97	Days 3,4,5,6 ,7	7	TBM
AP-C-9E03	A Phase2/3 Investigator-blind, Randomized, Parallel-group Study to Determine the Effects of Amlexanox Disc, 2 mg, (Early Formulation) on the Healing of Recurrent Aphthous Ulcers as Compared with Vehicle Discs or No Treatment	157	163	81	Days 3,4,5,6 ,7	7	Early
AP-C-2U108	An Open-Label, 28-Day Study to Evaluate the Long-term Safety of Amlexanox mucoadhesive Patch, OraDisc™ A 2 mg, in Patients with Recurrent Minor Aphthous Ulcers	106	0	0	Days 8, 15, 22, 29	28	TBM
Pharmacokinetics/Pharmacodynamics Trials							
AP-C-9E01	A phase 1, double-blind, randomized, vehicle-controlled study to Determine the Effects of Amlexanox OraDiscA, 2 mg, on healing of punch biopsy-induced wounds of the oral mucosa in healthy volunteers	11	9	20	1,2,3,6 ,8,10	10	Early
AP-C-1U107	A phase 1 study to investigate the pharmacokinetic characteristics of Amlexanox OraDiscA 2 mg, in 18 subjects with minor aphthous ulcers after a single application to 1 – 3 aphthous ulcers	18	0	0	0, 0.5, 1, 2, 3, 4, 6, 8, 10,12, and 24 hours post-dose	1	TBM

4.3 Review Strategy

Sources used for writing this review include all of the clinical studies listed above as well as results of studies submitted to NDA 20-511, Aphthasol (amlexanox 5% paste), and data from amlexanox 50-mg oral tablets. Only one of the clinical trials, AP-C-1U106 is considered a pivotal trial as was discussed in Section 2.5. The results of Study AP-C-9E03, a Phase 2/3 trial which used an older formulation, were examined to help clarify two review issues. One review issue is that one of the primary outcome variable

requirements for approval is demonstration of non inferiority of the vehicle to no treatment, which was borderline in its outcome in the pivotal trial. The second review issue was the efficacy question in children, which was inconclusive in the pivotal trial and therefore the pediatric data from the Phase 2/3 trial were also evaluated (Both to be discussed in detail Section 6.1.4).

The open label safety trial (AP-C-2U108) was the only trial which enrolled sufficient numbers of subjects for a long enough period to time to examine safety for chronic use; however, all subjects in all trials were monitored for safety and included in the safety reporting and analysis. Additional safety information was gathered from a review of results from the drug approvals and post-marketing information for Aphthasol paste and amlexanox 50-mg oral tablets. Approximately 800 subjects were treated with Aphthasol in clinical trials as a part of its development prior to the approval of its NDA. Post-marketing monitoring has included reports of adverse events between 1997 and the present. Over 1100 subjects were involved in pre-approval clinical studies in Japan in which the 50-mg tablets were administered for the treatment of asthma and allergic rhinitis. Data were collected for approximately 6400 patients from post-marketing safety surveys in Japan. The sponsor relied upon much of the biopharmaceutics evaluation of amlexanox from their studies conducted as part of their NDA submission for Aphthasol. Finally, data from Aphthasol and amlexanox tablets were submitted to help create the pharmacokinetics profile of Amlexanox.

4.4 Data Quality and Integrity

Early in the review process, a discussion between the Review Division and the Division of Scientific Investigations (DSI) was held to discuss the need for a site visit to audit any of the applicant's data and/or analyses. The discussion focused upon OraDiscA as a new delivery system for an identical dose of a drug that was approved in 1996 for the identical indication. Initial review of results from the various sites did not produce questions of unusual results at any particular center. The decision was mutually made that DSI would not schedule a site visit unless irregularities appeared as the review progressed. Similarly, there was no need for the review team or others (e.g., consultants, special government employees) to audit the case report forms (CRFs) or clinical source data.

4.5 Compliance with Good Clinical Practices

The content of the informed consent form was adequate and the sponsor obtained consent before enrollment into the trial as specified in the protocol. In terms of protocol violations, there were 18 subjects in the pivotal trial who had protocol violations, 15 of which were use of prohibited medications. One subject used two patches at each ulcer site, and was withdrawn from the study. One subject was diagnosed as having a Herpes Simplex Virus lesion, rather than an aphthous ulcer and was withdrawn form the study. One patient was randomized out of sequence. Fifteen subjects used medications during the study that were prohibited by the protocol, primarily oral analgesics – they were excluded from the efficacy evaluation.

One consideration that caused some discussion within the Division dealt with seven of the sites in the Phase 2/3 trial which were repeated in the pivotal trial, including use of the same investigators. The concern was that seven of the 23 sites used for the pivotal trial would have investigators who had already conducted this trial before, and therefore had the potential through their additional experience to give different outcomes than the remaining 16 sites. There was also concern that subjects may have been used twice at these sites. Evaluation of the results showed that no subjects who participated in the pivotal trial had participated in the Phase 2/3 trial. Nonetheless, the statistical reviewer did an analysis of the outcomes, examining results from the repeated sites separately. Interestingly, eliminating those seven sites from the overall analysis increased the success of the outcome of the pivotal trial significantly. The seven sites actually had results that had a greater "no treatment" effect than the other 16 sites. Because the pivotal trial was well-blinded and randomized, it is difficult to see how the investigators would be biased in their reporting.

4.6 Financial Disclosures

The sponsor has submitted to the NDA a completed and signed HHS Form FDA 3454 (Rev 6/02). In doing so, they have certified that "I have not entered into any financial arrangement with the listed clinical investigators whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a)." All investigators who participated in any of the trials during the IND development are listed. These arrangements do not raise questions about the integrity of the data.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

To assess the pharmacokinetics of OraDiscA, the Sponsor has conducted a Phase 1 single dose study (AP-C-1U107), a phase 1 pharmacology safety study to evaluate the effects of amlexanox on cytochrome P450, and a Phase 3 multiple dose study (AP-C-1U-106). In addition, clinical safety data of amlexanox from the oral paste and tablet formulations were supplied in this submission.

The basics of the pharmacokinetics of amlexanox were determined in the studies with amlexanox tablets. Systemically absorbed amlexanox is metabolized by hydroxylation to form the M-1 metabolite and some unidentified conjugates. The levels of M-1 metabolite were approximately 10% of the levels of amlexanox. There was no evidence of any accumulation of amlexanox or M-1 with multiple dosing. After a single oral application of 5 mg amlexanox, maximal serum levels of approximately 120 ng/ml were observed at 2.4 hours. Most of the systemic absorption of amlexanox is via the gastrointestinal tract, and the amount absorbed directly through the active ulcer is not a significant portion of the applied dose. The half-life for elimination was 3.5 ± 1.1 hours in healthy individuals.

Study AP-C-1U07 supplied the following pharmacokinetics profile of OraDiscA in an adult population after a single application as follows:

Mean Pharmacokinetic Parameters Phase 1 Study AP-C-1U107

Parameter	One Patch 2 mg	Two Patches 4 mg	Three Patches 6 mg
Cmax (ng/mL)	N=14	N=1	N=3
Mean ±SD	45.4±39.6	138	168.3±191.5
Median (range)	39.8 [ ]		79.9 [ ]
Tmax (hr)	N=13	N=1	N=3
Mean ±SD	2.8±1.7	3	3.0±1.0
Median (range)	2 [ ]		3 [ ]
T_{lag} (hr)	N=13	N=1	N=3
Mean ±SD	1.0±0.6	1	1.0±0.9
Median (range)	1 [ ]		0.5 [ ]
AUC_{0-24} (ng·hr/mL)	N=14	N=1	N=3
Mean ±SD	258±238	475	605±356
Median (range)	226 [ ]		584 [ ]
$T_{1/2}$ (hr)	N=7	N=1	N=3
Mean ±SD	4.5±2.0	3.2	8.8±3.5
Median (range)	4.5 [ ]		10.3 [ ]

Based on the reported T_{lag} (0-1 hr) and mean T_{max} (~ 3 hours), there appears to be no or little absorption of amlexanox rapidly and directly through the aphthous ulcers. The lag time and T_{max} values indicate a slow erosion of OraDiscA, and a slow systemic absorption of amlexanox from the drug product.

Pivotal Trial AP-C-1U106 measured serum levels of amlexanox after multiple applications of OraDiscA. It also allowed subgrouping to examine pediatric pharmacokinetics and the difference between 1, 2, and 3 patches placed concurrently. The number of subjects in the adolescent population is too small (N=3) to give any statistically meaningful conclusion with respect to overall exposure of amlexanox in this population. Nevertheless, the mean amlexanox concentration in this group exhibits a similar trend to those in the adults.

Appears This Way
On Original

Mean Pharmacokinetic Parameters, Phase 3 Study AP-C-1U106

Treatments	Amlexanox Serum Concentrations (ng/mL)	
	Prior to First Dose on Day 4	Two hours after First Dose on Day 4
All Patients		
Mean SD	16.0 ±31.7 (N=31)	20.9 ±24.1 (N=29)
Median (Range)	6.6 [ ]	14.8 [ ]
Pediatric Patients (N=3)		
	3.7± 5.2 (0-11.0)	13.5±12.3 [ ]
Patients Treated with One Patch, 4x daily		
Mean SD	9.8±16.5 (24)	15.8±16.4 (N=24)
Median (Range)	5.6 [ ]	11.5 [ ]
Patients Treated with Two Patches, 4x daily		
Mean SD	43.9±68.5 (N=5)	44.4±42.7 (N=5)
Median (Range)	10.0 [ ]	35.4 [ ]
Patients Treated with Three Patches, 4x daily		
Mean SD	20.4 (N=2)	18.6 (N=2)
Median (Range)	20.4 [ ]	18.6 [ ]

Approximately 17% of the dose is eliminated into the urine as unchanged amlexanox, a hydroxylated metabolite, and their conjugates. With multiple applications four times daily, steady state levels were reached within one week, and no accumulation was observed with up to four weeks of usage.

The effects of amlexanox of CYP450 19, 1A2, 2C19, 2D6 and 3A4 were less than 10% inhibition or stimulation. Thus, amlexanox is unlikely to have an effect on drugs or xenobiotics metabolized by those cytochrome P450 components. In addition, based upon the half-life of amlexanox (3-6 hours) and minimal renal elimination (17%), there is no significant safety concern in patients with renal or hepatic limitations for topical q.i.d. administration of OraDiscA.

5.2 Pharmacodynamics

The proposed mechanism of action is through histamine and leukotriene blockers. An early pharmacodynamics study showed that OraDiscA increased the rate of healing of biopsy wounds compared to contralateral wounds that received no treatment. However no pharmacodynamics studies were conducted to study the mechanism of action. Similarly, based upon the biopharmaceutical studies conducted for the approval of Aphthasol, there is no known effect of amlexanox on the QT interval and no know orthostatic effects or pharmacodynamic interactions. Therefore, no new studies were documented under this IND to evaluate those effects.

5.3 Exposure-Response Relationships

Based on NDA 20-511 for amlexanox paste, no new information has been submitted for the exposure-response relationships for the current mucoadhesive patch dosage form. The pharmacokinetics and pharmacodynamics of OraDiscA are consistent with those of Aphthasol. Since the dosing of drug substance is identical in OraDiscA to Aphthasol, the exposure-response relationships for efficacy are expected to be comparable to those in Aphthasol.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication – Aphthous Ulcers

Treatment of [ ] Aphthous Ulcers in Adults and Adolescents 12 years of Age and Older.

6.1.1 Methods

As was discussed in Section 2.5 of this review, only one pivotal trial is needed to support the efficacy component for the proposed indication, since OraDiscA is a new delivery system that contains the same active ingredient, at the same concentration, of an already marketed drug. This study, identified by the sponsor as AP-C-1U106, is a Phase 3 investigator-blind, randomized, placebo controlled trial which enrolled 701 subjects at 26 independent study sites.

The sponsor identifies Study AP-C-9E03 as a Phase2/3 trial. This study was conducted prior to the pivotal trial, and used an earlier formulation of the OraDiscA. Refer to section 2.5 of this review for a description of the differences in formulation and how the decision was made to consider this trial non-pivotal. Nonetheless, this earlier study has value in evaluating efficacy, as the protocols are nearly identical in both studies in study design, inclusionary and exclusionary criteria, endpoints, and results. In particular, the results from Study AP-C-9E03 will be persuasive in confirming the non-inferiority of the vehicle as will be discussed in detail in section 6.1.4.

6.1.2 General Discussion of Endpoints

The primary efficacy variable was identified in the protocol as the percentage of subjects who had healed (defined *a prioi* as all ulcers reaching the size of 0 mm) after 4 days of treatment (Day 5 of the study). In addition to the healing rate, pain resolution was also analyzed; however, as agreed upon during the End of Phase 2 meeting, pain resolution was identified as a secondary efficacy variable.

This choice of primary and secondary endpoints was based largely upon the conclusions of the trials of the previously approved amlexanox-containing product, Aphthasol. The clinical trials for Aphthasol employed both pain and healing as co-primary endpoints. Although the drug was approved based on a win of both, the pain relief results were difficult to interpret. Significant pain relief occurred on sporadic days during the trial,

and did not always correlate with significant healing as measured by ulcer size. To accurately reflect the outcome of the trials, the Aphthasol label states that "Pain relief occurred in conjunction with healing of the ulcers. Amlexanox oral paste, 5%, by itself, was not shown to be an analgesic medication." Based upon this past regulatory decision that amlexanox is not an analgesic, the Agency suggested that the sponsor use the percentage of subjects with complete healing as the primary outcome for OraDiscA, and evaluate the pain outcome as a sequel to the healing, and therefore secondary. The validity of the primary endpoint, percentage of subjects healed, was established during the approval process for Aphthasol. Data were submitted for related outcomes including comparison of the mean ulcer size between groups during the early days of the trial, and time to complete healing. Both of these analyses corroborated the result from the primary outcome variable.

Clinical benefit of the outcome was discussed at length during the deliberations on Aphthasol, and what was learned from that was applied during the regulatory process for OraDiscA. A clinically meaningful effect was not pre-specified in Aphthasol; any statistically significant improvement in the percentage of subjects healed with Aphthasol compared to vehicle was judged acceptable for approval. The relatively modest improvement in healing time seen (37% of subjects healed with Aphthasol compared to 27% of vehicle subjects healed at Day 4; average improvement in time to healing with Aphthasol was 1.6 days) was not a roadblock to approval since the safety profile for amlexanox is very good. For consistency between Aphthasol and OraDiscA, in which the same dose of amlexanox is proposed for the same indication, the same philosophy will apply to OraDiscA. The labeling will report the magnitude of effect, allowing the prescribing clinician and patient to make comparisons between the OraDiscA and Aphthasol, based upon their labels.

Access was advised very strongly by the Division to include a "no treatment" arm in the pivotal trial in addition to the vehicle arm, which they did. As was seen in the analysis of the Phase 2/3 trial, a vehicle possesses potential therapeutic value as a barrier to prevent insult to the ulcer. This vehicle could therefore affect the healing (primary endpoint) as well as pain relief (secondary endpoint) because of its ability to shield the ulcer. The agreement at the EOP2 meeting was that to demonstrate efficacy, the results would need to show a statistically significantly greater percentage of subjects who healed in the OraDiscA group compared to the vehicle group. It was also agreed that for an efficacy win, the placebo arm would have no worse efficacy than the no treatment arm. This was required to rule out the possibility that the OraDiscA arm could be superior to the vehicle arm due to the disk component of the total product causing irritation to the ulcer site, thus overstating the effect from the OraDiscA. The sponsor stated in a 45-day SPA that "the non-inferiority of vehicle to no treatment will be established if the lower confidence bound exceeds -8%."

The sponsor chose Day 5 as the time point for the primary endpoint evaluation largely as a result of reviewing Aphthasol's outcome and looking at early OraDiscA trials for the time to optimal improvement. Although this outcome seems appropriate, it is not without

potential shortcomings. For example, since the baseline requirement is an ulcer which has developed within 36 hours, there is the potential variation in subjects of 1.5 days for the baseline progression of ulcers, and that assumes that the self-reporting is always accurate. Therefore, an ulcer that has been present for 36 hours at baseline is quite likely to be healed by Day 5, even in the no treatment group. In addition, not all ulcers are the same size. Larger ulcers take longer to heal, so that a larger than average ulcer has a much smaller chance of healing by Day 5, and would be regarded as a failure, even if its healing rate is much better than a comparably sized ulcer on no treatment or vehicle. Randomization should minimize this potential problem by balancing the groups so that the sizes of the ulcers at baseline and the time at which the ulcer first appeared are evenly balanced.

In addition to this primary analysis of healing, the sponsor also proposed a secondary analysis of healing as corroboration and two other secondary endpoints which measure pain response. The alternative evaluation of healing is an analysis of time-to-healing, based on reaching ulcer size of 0 mm^2. Time-to-healing is defined for each patient as the number of days until healing if the ulcer healed on or before Day 7, or as a right-censored observation if the ulcer did not heal on or before Day 7. The time-to-healing distributions were compared among the three treatment groups using survival analysis as a secondary efficacy analysis.

The other two secondary efficacy variables are the percentage of patients with complete resolution of pain on study day 5 (defined as having reached pain score of <5 mm), and the time to healing based on pain score. To record the reduction in pain, subjects marked a 100-mm visual analogue scale (VAS) twice a day, which was anchored with a 0 at the far left for no pain, and a 100 at the far right for "worst pain imaginable."

6.1.3 Study Design

The pivotal trial, AP-C-1U106, meets the regulatory definition of adequate and well-controlled. The design, if executed according to protocol, is capable of assessing the benefit of OraDiscA. With respect to adequate and well-controlled studies, the trial:

1. Has minimal bias.
   The study has an OraDiscA group, a vehicle disk group, and a no treatment group. Although the subjects in the no treatment group could not be blinded, the evaluator does not know any individual subject's status. The primary outcome variable, measurement of ulcer size, is very objective and there is very little that the subject could do to influence this outcome. What is important is that the clinician who measures the size of the ulcer is blinded. Also helpful in minimizing bias is the presence of both a vehicle group and a no treatment group, so that the comparison of the vehicle to the OraDiscA group is blinded to both subject and investigator. The pain measurement is subjective, however, so that bias is quite likely between the no treatment group and the other two. As with the primary outcome evaluation, the presence of a vehicle group in addition to no

treatment allows a double-blinded comparison to assess the actual contribution from the active drug.

The win is set as the superiority of OraDiscA to vehicle disc. For non-inferiority testing, the vehicle is tested against no treatment with the purposes of demonstrating that the vehicle does not make the ulcer worse. It is unlikely that the subjects' knowledge of no treatment would influence the healing of the ulcer to any significant extent.

2. Has an adequate choice of control group
As was discussed in 6.1.2, the choice of primary and secondary endpoints was based upon results of Aphthasol studies and early OraDiscA trials. The OraDiscA studies did not need to rely on an historical control.

With respect to assessment of benefit, the pivotal trial:

1. Was of adequate duration
Seven days is the average length for healing of an aphthous ulcer. At baseline, an inclusion criterion dictated that the ulcer had to have developed within 36 hours. Since aphthae spontaneously heal in an average of one week, one would expect the difference between groups to become smaller as the end of the 7-day trial period approached, since the natural progression of the disease produces healing regardless of treatment. A trade-off had to be reached between giving the product sufficient time to have an effect, but not too much time, or the effectiveness would be difficult to determine. Based upon the greatest difference between groups being reached on Day 5 of the Aphthasol study, this time point was chosen by the applicant to be the time point for the primary outcome analysis for OraDiscA. One open label trial of 28 days duration was conducted to simulate several back-to-back treatment periods, but no efficacy measures were made during that trial. Those results will be discussed in the safety section of this review.

2. Employed Appropriate Entry criteria.
Patients were screened for the presence of aphthous ulcers and accepted only if the ulcer had appeared within 36 hours, which is appropriate for this proposed indication. Since it is not uncommon for patients to have concomitant ulcers (95% of chronic aphthous sufferers have reported having up to 3 aphthous ulcers concomitantly), subjects were enrolled with up to 3 ulcers.

3. Adequately chose the dosing
The dose chosen for OraDiscA was identical to the dose for aphthosol. The 2 mg of amlexanox in each OraDiscA corresponds to the approximate amount of amlexanox in one dab of 5% amlexanox paste, which is currently marketed in the United States. The proposed frequency of four times per day is also identical to the frequency that was proved efficacious for the amlexanox paste; the sponsor suggests that this is the highest frequency with which patients are likely to

comply. It would have been ideal to experiment with lower doses since it was expected that this OraDiscA new delivery system would be more efficient than the paste at supplying the same amount of amlexanox to the site and retaining it there longer. Nonetheless, amlexanox was shown in Aphthasol to have a very safe profile, and the Agency had no comments during the IND phase of development about exploring other dosing.

6.1.4 Efficacy Findings

In this section of the review, a detailed review of the results and analyses of the clinical studies that provide efficacy data for the proposed indication will be presented. A discussion of the demographic, baseline characteristics and inclusion/exclusion criteria pertinent to the efficacy evaluation is also included. The findings from the statistician's analysis of the data are integrated into the discussion. This section also includes a review of effectiveness data for gender, age, and racial subgroups.

The section also addresses limitations of the efficacy studies and describes how they have been resolved. For example, successful demonstration of safety and efficacy from one pivotal trial, 1U106, is sufficient for approval, as has been explained in Section 2.5, with reference to the FDA guidance for industry on *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*. However, the results of Study 9E03, a Phase 2/3 study (sometimes referred to in this review as a non-pivotal phase 3 trial), is referenced in cases where the pivotal trial results alone are not conclusive.

Percent of Subjects healed on Day 5 - Primary Outcome variable

The primary outcome variable as pre-stated in the protocol is the percentage of patients who had healed (all ulcers size of 0 mm^2) after 4 days of treatment (Day 5 of the study). To win on this, it was agreed that there would be a statistically significantly greater percentage of subjects who were completely healed in the amlexanox group compared to those in the vehicle group. There must also be a demonstration that the outcome from the vehicle group is non-inferior to outcome in the no treatment group. The Pairwise comparisons of Day 5 healing rate were analyzed using the Cochran-Mantel-Haenszel test. Below is a summary table of this outcome variable:

Percentage of Patients with Complete Ulcer Healing on Day 5
Studies 9E03 and 1U106

Study (duration)	Study site	Amlexanox (A)	Vehicle (V)	No-treatment (N)	Comparison[1]	p-value or LL
9E03 (6/00 – 12/00)	Overall	76/157 (48.4%)	58/163 (35.6%)	23/81 (28.4%)	A vs. V LL for V vs. N[2]	0.026 -5.6%
1U106 (6/02 – 3/03)	Overall	92/303 (30.4%)	66/301 (21.9%)	21/97 (21.7%)	A vs. V LL for V vs. N[2]	0.015 -9.2%

Source: Statistical Reviewer's analysis based on the sponsor's electronic SAS data sets.
[1] Comparison of A vs. V is based on CMH test adjusting for study site; the comparison of V vs. N is based on the lower limit of one-sided 97.5% confidence interval for (vehicle – no-treatment).
[2] LL for V vs. N is the exact lower limit of one-sided 97.5% confidence interval computed using StatXact version 5.

Although both studies have met the test of statistical significance for the percentage of subjects healed on OraDiscA compared to vehicle at Day 5, it is worthwhile to examine the pattern of healing during each of the seven days for purposes of completeness.

Number (%) of Patients with Complete Ulcer Healing Over Time (ITT) – Study 1U106

Time	Amlexanox (n = 303)	Vehicle (n = 301)	No-treatment (n = 97)
Day 3	20 (6.6%)	13 (4.3%)	3 (3.1%)
Comparison[1]			
Amlexanox vs. Vehicle	0.192		
Amlexanox vs. No-treatment	0.179		
Vehicle vs. No-treatment	–2.91%		
Day 4	57 (18.8%)	40 (13.3%)	10 (10.3%)
Comparison[1]			
Amlexanox vs. Vehicle	0.055		
Amlexanox vs. No-treatment	0.050		
Vehicle vs. No-treatment	–4.18%		
Day 5	92 (30.4%)	66 (21.9%)	21 (21.6%)
Comparison[1]			
Amlexanox vs. Vehicle	0.015		
Amlexanox vs. No-treatment	0.093		
Vehicle vs. No-treatment	–9.16%		
Day 6	115 (38.0%)	107 (35.6%)	35 (36.1%)
Comparison[1]			
Amlexanox vs. Vehicle	0.535		
Amlexanox vs. No-treatment	0.695		
Vehicle vs. No-treatment	–11.52%		
Day 7	154 (50.8%)	159 (52.8%)	47 (48.5%)
Comparison[1]			
Amlexanox vs. Vehicle	0.560		
Amlexanox vs. No-treatment	0.627		
Vehicle vs. No-treatment	–7.06%		

Source: Sponsor's NDA submission (Module 5, Vol.1.3, pages 61 and 132-133). Note that the table is intended to observe efficacy trend, otherwise, a multiplicity adjustment would be needed.

[1] The comparison (p-value) of amlexanox vs. vehicle and amlexanox vs. no-treatment each was based on CMH test adjusting for investigator. The listing for the comparison between vehicle and no-treatment was the lower limit of one-sided 97.5% confidence interval of the treatment difference (i.e., vehicle – no-treatment).

Note that the effect is the strongest at Day 5 as the sponsor had predicted. At the last day of the trial, Day 7, the difference between the treatment and vehicle groups had actually disappeared and is trending in the wrong direction. Early in the review process, the sponsor was asked about the Day 7 data and explained it in a separate submission to the NDA. They stated that as time progresses, the difference in percentage of subjects healed will lessen between groups due to the natural progression of healing. Without seeing data from the days after Day 7, it is difficult to predict the remainder of the trend. Nonetheless, it is somewhat disconcerting that this difference had disappeared by the time that only half of the subjects had been healed.

Non-inferiority of vehicle to no treatment

The second requirement for a win on the primary outcome variable is that the percentage of healed individuals in the vehicle group is not inferior to the percentage of healed subjects in the no treatment group. This stipulation was included to rule out the possibility that the vehicle makes the ulcer worse and is discussed in FDA's Clinical/Medical Guidance document entitled, Chronic Cutaneous Ulcer and Burn Wounds – Developing Products for Treatment (Draft Issued 6/2000). During the 45-day special protocol assessment, the sponsor proposed that non-inferiority would be achieved if the lower limit of the 97.5% confidence interval around the difference between groups is greater than -8%. In the statistical review of this proposal, the reviewer acknowledged that this was acceptable.

As is seen in the summary table at the beginning of this section, the actual value of the confidence interval's lower limit in the pivotal trial was -9.2%. Because this -8% value was proposed by the sponsor, rather than the Agency, and the actual -9.2% value was very close, we must consider whether the value is sufficiently higher to raise a concern about the vehicle disk making the aphthous ulcer worse. It is worthwhile in a situation that is very close such as this, to look at other relevant comparisons, including the results from the Phase 2/3 trial. Because prior studies, including the Phase 2/3 trial had shown a difference of approximately 10% between the vehicle arm and no treatment in the percentage of subjects healed at Day 5, the sponsor used those values for the power calculation. In the pivotal trial, the actual difference on Day 5 was less than 1%. The no treatment arm, while sufficiently powered to detect the difference between active and vehicle, was not able to reach the -8% confidence interval as predicted. However, there is also no evidence to suggest that the vehicle arm had worse efficacy than no treatment (pivotal trial value 27% vs. 26%).

In the Phase 2/3 trial, (see chart at the beginning of this section) the percent of subjects healed for the vehicle arm is 8 percentage points greater than no treatment, and the lower confidence interval for that non-inferiority testing was -5.7%, well less than the 8% value set for the pivotal trial. The Phase 2/3 trial, however, is not viewed as pivotal because of the difference in formulation as was discussed earlier in this review. Although the efficacy of the OraDiscA cannot be considered pivotal due to an additional backing layer which the Agency was concerned would keep the amlexanox in contact with the ulcer longer than the older formulation without the backing, the vehicle does not contain any

amlexanox. Therefore, the effect of the vehicle disk, if negative, would be just as likely to show up in the old formulation as the new, since the adhesive layer is identical in both formulations.

One other piece of information that is also helpful in determining if the vehicle is contributing to making the ulcer worse is to examine the AE profile for local irritation in both the OraDiscA and vehicle groups. The AE profile will be discussed in detail in Section 7.1.5.4 in this review and will show that the percentages are identical in reporting irritation (1.2% for both), and very similar between the two in terms of pain, burning, paresthesia, and reaction NOS. If the vehicle negatively affected the healing of the ulcer, one might observe an increase in local irritation resulting from the placebo.

This additional information from the phase 2/3 trial coupled with the sponsor's very close miss to their own non-inferiority margin is sufficient to conclude that the vehicle has little or no negative impact on efficacy.

Secondary Analysis of Healing – Time to complete healing

The secondary analysis of ulcer size healing is the time to complete healing. Since the sponsor won on percentage of subjects healed on Day 5, a win on this endpoint is not required, but may be helpful in labeling not only for additional comprehension for patients and clinicians but also to be able to compare this to Aphthasol's labeling, which includes it. The data demonstrated a statistically significant difference between the OraDiscA and vehicle (log rank test p=0.034) as well as a statistically significant difference between the OraDiscA and no treatment (log rank test p=.003). However, because the sponsor used median time rather than mean time (as was measured in the Aphthasol trials), it is a not possible to calculate a meaningful mean number of days until healing for each group.

Pain Reduction

The other two secondary outcome variables are measurements of pain reduction. The first is percentage of subjects to achieve pain resolution at Day 5, which is defined as choosing a score of < 5mm on the VAS pain scale. The chart that follows shows not only the comparison of groups at Day 5, but also at the other days of the trial to verify the consistency of this pattern. At every day, including Day 5, the OraDiscA was significantly better than no treatment, but at no day, including Day 5, did OraDiscA demonstrate statistical superiority over the vehicle patch. This is not a surprising finding, as the vehicle patch, by virtue of covering the site and protecting it from insult would be expected to contribute to pain reduction. This confirms that OraDiscA reduced pain, but that amlexanox does not significantly contribute to the pain reduction by itself. The labeling will need to address the fact that the patient may expect pain relief from the entire OraDiscA product, but may not imply or state that the amlexanox alone is producing this effect.

Pain resolution based upon VAS – Cumulative Numbers and Percentages ITT population

Study Day	Amlexanox OraDiscA	Vehicle Patches	No treatment	P value
Day 2, afternoon	23 (7.6%)	16 (5.3%)	1 (1.0%)	0.052
Day 3, afternoon	53 (17.5%)	51 (16.9%)	8 (8.3%)	0.08
Day 4, afternoon	91 (30.0%)	90 (29.9%)	23 (23.7%)	0.44
Day 5, afternoon	134 (44.2%)	132 (43.9%)	30 (30.9%)	0.045
Day 6, afternoon	171 (56.4%)	166 (55.2%)	42 (43.3%)	0.058
Day 7, afternoon	186 (61.4%)	193 (64.1%)	51 (52.6%)	0.12

The other analysis of pain relief, time to complete pain resolution, confirms the above results. In that analysis, the survival analysis for the ITT population demonstrated that the amlexanox treatment group had a statistically significantly shorter median time to pain relief than the no treatment group (5.0 days compared to 6.0 days; log rank p =0.034, Wilcoxon p = 0.016.) The vehicle group was also significantly better than no treatment in pain relief (log rank p = 0.053, Wilcoxon p = 0.041). There was no difference between the amlexanox group and the vehicle group (Both groups had a value of 5.0 days)

Effectiveness for Subgroups – Age, Race and Gender.

Demographically, gender, age and ethnicity data were analyzed by study and by treatment group and are summarized in the table below. Of note is that the groups are balanced for the important demographic characteristics that have the potential to bias the results. Specifically, the mean and median age are nearly identical between all three test groups. The racial breakdown is very similar between all test groups, although Caucasians are slightly underrepresented in the no treatment group, and Hispanics are slightly overrepresented in the no treatment group. Nonetheless, the overall comparison of race produces a p value of 0.60, indicating no significant findings of non-randomness. It must be noted that the percentage of Caucasians (86%) is slightly higher than the overall US population and the African-American population is slightly lower than the overall US population. (2000 Census – 83% Caucasian, 13% Black, 9% Hispanic). Significantly more female than male subjects were enrolled with an almost 3:1 ratio. Although epidemiologic data supports a higher prevalence of aphthous ulcers in females (approximately 55% of aphthous ulcer sufferers are female), the 2:1 ratio of enrollment is higher than predicted. In addition to prevalence, the high ratio reflects the greater propensity of women to seek medical care and to enroll in clinical trials. The mean age for subjects enrolled in the pivotal trial (29.7 years) is lower than the US population (35.8 years)

Subjects were enrolled into the study with 1, 2, or 3 aphthous ulcers. The percentage of each baseline number was adequately randomized between treatment groups. As is expected with recurrent aphthous ulcers, approximately 73% of all subjects had one aphthous ulcer. Approximately 19% presented with two aphthous ulcers, and approximately 8% had three ulcers.

Baseline Characteristics

		Amlexanox OraDiscA	Vehicle Patches	No Treatment	p-value
		N = 303	N = 301	N = 97	
Gender	Female	196 (64.7%)	202 (67.1%)	60 (61.9%)	0.61
	Male	107 (35.3%)	99 (32.9%)	37 (38.1%)	
Age	Mean (S.D.)	29.7 (12.2)	28.9 (12.4)	29.7 (12.4)	0.66
	Median [Range]	26 [12 – 75]	26 [12 – 73]	26 [12 – 68]	
Race	Caucasian	265 (87.5%)	259 (86.0%)	77 (79.4%)	
	Hispanic	21 (6.9%)	22 (7.3%)	11 (11.3%)	
	Black	6 (2.0%)	7 (2.3%)	2 (2.1%)	0.60
	Asian	5 (1.7%)	7 (2.3%)	2 (2.1%)	
	Other/Mixed	6 (2.0%)	6 (2.0%)	5 (5.2%)	
No. of Ulcers Treated Daily During Study					
	1 ulcer	219 (72.3%)	231 (76.7%)	68 (70.1%)	0.63
	2 ulcers	58 (19.1%)	50 (16.6%)	21 (21.6%)	
	3 ulcers	26 (8.6%)	20 (6.6%)	8 (8.2%)	

It should be noted that the studies were not designed to test efficacy within subgroups, but rather to explore trends. There has been no past evidence that patients respond differently to amlexanox based upon age, race or gender. More than 80% of the subjects are Caucasian, and their ulcer healing rates are similar to those based on the overall results. The Hispanic subgroup of approximately 8% showed the same outcome as Caucasians. The Asian and Other subgroups had a small percentage with wider variation, so any conclusions about treatment comparisons are not possible.

In the remainder of this section, the efficacy results by subgroup will be discussed. The following table presents the results from the pivotal trial with stratification by subgroup for age, race, gender, and number of ulcers treated.

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Subgroup Results of Complete Ulcer Healing Rate on Day 5 (ITT)

Study 1U106

Subgroup	Amlexanox (n = 303)	Vehicle (n = 301)	No-treatment (n = 97)
Overall	92/303 (30.4%)	66/301 (21.9%)	21/97 (21.6%)
Age			
Pediatric (12 – 17 years)	11/37 (29.7%)	13/49 (26.5%)	4/12 (33.3%)
Adult (18 – 64 years)	78/263 (29.7%)	53/248 (21.4%)	17/84 (20.2%)
Geriatric (65 and older)	3/3 (100%)	0/4 (0%)	0/1 (0%)
Gender			
Male	30/107 (28.0%)	16/99 (16.2%)	7/37 (18.9%)
Female	62/196 (31.6%)	50/202 (24.8%)	14/60 (23.3%)
Race			
Caucasian	83/265 (31.3%)	55/259 (21.2%)	16/77 (20.8%)
Black	2/6 (33.3%)	2/7 (28.6%)	1/2 (50%)
Hispanic	5/21 (23.8%)	4/22 (18.2%)	1/11 (9.1%)
Asian	0/5 (0%)	3/7 (42.9%)	1/2 (50%)
Other	2/6 (33%)	2/6 (33%)	2/5 (40%)
Number of treated ulcers			
One	80/219 (36.5%)	59/231 (25.5%)	19/68 (27.9%)
Two	10/58 (17.2%)	4/50 (8.0%)	1/21 (4.8%)
Three	2/26 (7.7%)	3/20 (15.0%)	1/8 (12.5%)

Source: Sponsor's NDA submission (dated 3/15/04, Module 5, Vol.5.1, pages 3-4) and sponsor's electronic SAS data set (LOGIT.xpt).

Men and women had differences in their responses to treatment. Overall, men had larger ulcer sizes at baseline than women, and as expected, not as many men reached total healing by Day 5. Stratification by gender does show consistency in the overall results - in both men and women, the OraDiscA group is superior to the vehicle group.

The results of the one and two ulcers at baseline are consistent with the overall results. However, for those subjects with 3 ulcers at baseline, the trend is that the OraDiscA is inferior to vehicle or no treatment. Because the numbers are very small in this subgroup, interpretation of these results is inconclusive.

For the breakdown by age in the pediatric group (12 – 17 years of age), the results show only a very slight improvement of the OraDiscA group over vehicle, and that the no treatment group fared best. The numbers in this subgroup of pediatrics however, is too small for adequate conclusions. In particular the no treatment group's results of 4/12 improvement would fit perfectly into the overall efficacy pattern with just one less

subject healed (3/12 or 25%). As a follow-up, pediatric efficacy was examined in the phase 2/3 trial as follows:

Subgroup Results of Complete Ulcer Healing Rate on Day 5 (ITT)

Study 9E03

	Amlexanox (n = 157)	Vehicle (n = 163)	No-treatment (n = 81)
Overall	76/157 (48.4%)	58/163 (35.6%)	23/81 (28.4%)
Age			
Pediatric (12 – 17 years)	3/12 (25.0%)	3/11 (27.3%)	3/4 (75.0%)
Adult (18 – 64 years)	71/142 (50.0%)	54/147 (36.7%)	20/76 (26.3%)
Geriatric (65 and older)	2/3 (66.7%)	1/5 (20.0%)	0/1 (0%)

Source: Sponsor's NDA submission (dated 3/15/04, Module 5, Vol.5.1, page 6) and electronic SAS data set (Diary_p.xpt).

Once again, the results of the pediatric group do not support the overall trend, but the numbers in this subgroup are too small to draw conclusions about effect. There is no biological hypothesis or supporting evidence that children would respond differently to amlexanox than adults. In addition, pediatric trials are always challenging, particularly in cases where compliance is an issue such as this one where the children would need to be placing new disks four times a day for 7 days. For further discussion of pediatric considerations and recommendations, see Sections 8.3 and 8.4 of this review.

For the geriatric subjects, the numbers are extremely small – a total of 8 geriatric subjects enrolled in the pivotal trial and 9 in the phase 2/3 trial. The trend in both is that the OraDiscA has superior efficacy to the vehicle and the no treatment groups, so although numbers are too small for conclusions, the data trend in the right direction.

Inclusion/Exclusion Criteria Pertinent To the Efficacy Evaluation

The inclusion criteria are appropriate and included male and female subjects ages 12 and above, a history of recurrent minor aphthous ulcers which take 5 days or more to resolve, and at least one ulcer that developed within the last 36 hours prior to screening. Exclusion criteria for the pivotal study include underlying conditions such as diabetes or uncontrolled infection which may interfere with the wound healing, or ulcerative colitis, Crohn's disease, or Behcet's syndrome which also produce oral ulceration. Individuals who wore a denture or orthodontic device that may come in contact with the ulcer were excluded as were individuals who use tobacco products. Individuals who were currently being treated with aspirin, NSAID steroid inhaler, or steroid nasal spray, or retinoids, or immunomodulatory agents were excluded.

The exclusionary conditions are reasonable, and were put into place to avoid confounding variables that may have biased the study results. For example, concomitant anti-inflammatory drug use may likely have a therapeutic effect on aphthous ulcers, making it

difficult to measure the true effect from the amlexanox. Likewise, the presence of diabetes, or the presence of an irritating intraoral appliance would negatively affect the ulcer healing. The impact of smoking on ulcer healing is unclear –data shows that smokers are actually at less risk of developing aphthae than non-smokers. It would be ideal to include these individuals, and distribute them evenly into the various treatment groups, allowing for subgroup analysis. Labeling may need to be crafted to include information about exclusion of some of the diabetics and tobacco users, who encompass a large percentage of the United States population.

6.1.5 Clinical Microbiology

Prior to NDA submission, a request was made to Clinical Microbiology via consult to determine if microbiologic activity was a feature of amlexanox. The clinical microbiologist responded that the medical literature using PubMed in August, 2001 found no references to antimicrobial activity of amlexanox correlated with acceleration of healing of aphthous ulcers. Since OraDiscA has no antimicrobial activity, no further clinical microbiology review was performed.

6.1.6 Efficacy Conclusions

The sponsor has adequately demonstrated that OraDiscA effectively increases the percentage of patients with aphthous ulcers who are healed compared to those who received a vehicle disk. They have also shown that the effect is valid, and was not caused by the vehicle exerting some detrimental effect on the aphthous ulcers.
The effect was also valid in individuals with up to 3 concomitant ulcers. The sponsor was not able to demonstrate that OraDiscA is more effective than vehicle in reducing pain; however, OraDiscA is significantly better than no treatment in reducing pain. The reduction of pain compared to no treatment was most likely due to the reduction of inflammation plus the barrier of the disk relieving pain, although this hypothesis was not specifically tested. The labeling should reflect that OraDiscA is not an analgesic but does help to relieve pain through reducing inflammation.

The pediatric subgroup analysis reveals a trend in the opposite direction in the evaluation of OraDiscA's efficacy. Although there are not large enough numbers to draw statistically sound conclusions, the reversal from the expected trend does not support efficacy in children. Because there is no biological reason to believe that children would not respond to OraDiscA, the trial as designed may have been unable to produce valid results.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

7.1.1 Deaths

No deaths occurred during any of the trials conducted with amlexanox mucoadhesive patch formulation or any other amlexanox formulations. There are no reports in the literature of death linked to amlexanox.

7.1.2 Other Serious Adverse Events

No serious adverse event was reported during any of the trials conducted with amlexanox mucoadhesive patch or during trials of any other amlexanox formulations submitted to this NDA.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

This summary chart includes clinical trials AP-C-1U106, AP-C-2U108, AP-C-9E03, and AP-C-9E02. The first two trials were performed on final formulation of OraDiscA, whereas the latter two were conducted on the earlier formulation.

Subject Withdrawal in AP-C-1U106, AP-C-2U108, AP-C-9E03, and AP-C-9E02

Reason for Withdrawal	Amlexanox Patches (N = 592)	Vehicle Patch (N = 490)	No Treatment (N = 178)
Worsening of Condition	2 (0.3%)	0	0
Adverse Event	4 (0.7%)	5 (1.0%)	0
Subject's Request	13 (2.2%)	4 (0.8%)	10 (5.6%)
Protocol Violation	6 (1.0%)	2 (0.4%)	0
Lost to follow-up	4 (0.7%)	1 (0.2%)	2 (1.1%)
Other Reason	2 (0.3%)	4 (0.8%)	0

Note that nine of the subjects in these four trials withdrew due to adverse events. Subjects who discontinue treatment in association with an adverse event receive special attention in regulations (their CRFs must be submitted) and their analysis is a critical part of the safety evaluation. In the next section of this review, the details regarding the adverse events associated with these subjects will be presented.

7.1.3.2 Adverse events associated with dropouts

Before examining the adverse events associated with dropouts, it must be considered that some of the subjects being evaluated for safety participated in trials that tested the early formulation of OraDiscA and some subjects participated in trials that tested the to-be-

marketed formulation (Refer to the discussion in Section 2.5 of this review for further details on the formulation differences). Although the active ingredient is identical in both formulations, the use of different backing materials raises a question of a potential difference in responses that could affect the safety profile. Therefore, the narrative of the withdrawals provided in this section will be differentiated by formulation group.

Final Formulation Trials
A review of the studies included in this summary chart reveals that of the 592 subjects exposed to amlexanox patches, 409 received final formulation patches. Of these 409, two subjects withdrew from the studies due to adverse events. One of the subjects developed increased redness at the application site and a rough texture of the oral mucosa and tongue starting on Day 4. Treatment was discontinued on Day 5 and the condition resolved by Day 7. The second subject developed nausea on Day 2 and stopped using the patches, whereupon the nausea resolved.

Four subjects in the final formulation trials who were assigned to the vehicle withdrew due to reported adverse events. One subject withdrew due to reported nausea after the first day of use, which resolved after discontinuation. Another subject reported lip swelling, nausea, intermittent headache and discomfort at the application site on Day 2 - the events resolved the same day, after discontinuation of the product. A third subject on final formulation vehicle developed itching on her face, eyes, ears and throat that began on Day 1; she discontinued the study drug and the event resolved later that day. The fourth subject reported pain and swelling of the lower lip close to the ulcer site. She was withdrawn from the study, and the pain and swelling resolved when the ulcers had healed on Day 11.

Early Formulation Trials
Two of the 194 subjects who received the early formulation withdrew due to adverse events. One subject had a 20-minute episode of increased heart rate and light-headedness after one day of treatment and stopped using the product. The second subject withdrew on Day 5 due to severe pain at the application site.

In the early formulation vehicle group, one subject withdrew from the study on the third day due to nausea. The nausea abated later on the third day.

The fact that these adverse events associated with dropouts are few, mild, and evenly distributed between the test group and the placebo is a good indication that there was not a pattern of discontinuation of use of the product resulting from adverse events. In terms of causality, it is possible that both the vehicle and the active disk are capable of causing localized irritation, nausea, or sensitization as reported in these dropouts. A full analysis of all adverse events reported in these trials will be discussed later in this review.

7.1.3.3 Other significant adverse events

Eight adverse events that occurred in the clinical trials did not lead to discontinuation but are considered significant and are described in this section. Significant adverse events

are defined by ICH as marked hematological, laboratory, or other abnormalities not meeting the definition of serious. Seven of the events occurred in the trials that used the new formulation and the other in a trial using the old formulation. In the trial using the old formulation, one subject assigned to the amlexanox patch experienced a rash on Day 3 on both cheeks. The examiner recorded light erythema, but no swelling or other evidence of inflammation. The subject declined to return to the study center for further investigation.

Of the seven subjects enrolled in final formulation trials, four who reported events were assigned to the amlexanox group, and three to the vehicle group. The subjects on active drug reported the following:

1. One subject recorded in her diary tongue soreness beginning on Day 5 and vesicles starting on Day 7. She did not mention these events to the investigators, and the investigator did not observe the events during visit examinations. The subject completed the 28-day study.
2. Another subject reported mild burning and mild redness at the patch application site, beginning on Day 26. The subject completed the 28-day trial and returned on Day 30 at which time the reactions had resolved.
3. A third subject reported redness and irritation at the application site after three days of treatment. The investigator noted that the aphthous ulcer had increased in size. The patient completed this 7-day study, although the investigator noted that on Day 7 the ulcer was still not improved. All events resolved on Day 10.
4. A subject reported mild bleeding at the application site on Day 5, which resolved on Day 6. The subject completed the 7-day trial.

Vehicle Disks:

1. One subject reported mild cheek swelling on Day 2 that resolved on Day 4; the subject completed the seven days of the study.
2. Another subject reported mild irritation and edema at the application site on Day 3, which resolved on Day 4. The subject completed the 7-day study.
3. A third subject reported an increase in size and pain related to the aphthous ulcer on Day 3. The subject completed the trial.

Laboratory testing was performed in one study only (AP-C-2U108); the tests were performed prior to the first application of amlexanox patch and during the last study visit after 28 days of treatments. None of the laboratory testing revealed marked hematological or other lab abnormalities that would warrant discussion in this section. In Section 7.1.7 of this review, laboratory testing will be described in full and any potential abnormalities discussed.

7.1.4 Other Search Strategies

There were no safety signals that arose from the sponsor-conducted studies that required construction of any algorithm involving combinations of clinical findings as a marker for

a particular toxicity. No pharmacologically-related drugs produced signals of such concerns. However, a concern about potential aspiration of the disk was raised by the Agency during the EOP2 meeting. In Section 7.1.12 of this review, the results of the sponsor's measure of erosion time and review of past safety data will be discussed.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

During all of the clinical trials, the Investigator questioned subjects at every visit about adverse events using an open question, and was instructed not to influence the subjects' answers. Subjects were also questioned at each visit to assess the reaction to patch application. The following two questions were asked at each visit:

> "Have you noticed any change in your health since the last visit?"
> "Did you experience any pain or discomfort when using the patches?"

All adverse events, either reported verbally by the patient or observed by the investigator, were transcribed onto the Case Report Form. On that form, events were reported as either "application site reactions" or general events.

An Adverse Event Form was completed for any subject starting a new concomitant therapy, other than vitamins, after enrollment into the study. A change in a concomitant therapy resulting from a change in the disease or medical condition for which the therapy is being taken was fully documented on the Concomitant Medication Form as well as by completion of an Adverse Event Form, when appropriate.

When an adverse event persisted at the end of the study, the Investigator ensured a follow-up of the subject until the Investigator/Sponsor agreed the event was satisfactorily resolved.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The sponsor grouped closely related investigator or subject reported terms using the MedDRA dictionary of preferred terms. One weakness of the dictionary is that there may be many related terms that may be used to describe an event. Though this "granularity" can result in missing a signal, this was not an issue in this case. From the pooled safety data from all clinical trials, the most commonly reported AE is application site reactions. Of 81 total application site reactions the MedDRA dictionary breakdown showed 39 for pain, 7 for irritation, 21 for burning, 8 for paresthesia, all of which matched the reporting on site. Reports from the six subjects that are listed in the table as application site reaction NOS is a result of the subjects not being more specific to the reporter.

7.1.5.3 Incidence of common adverse events

Adverse Events Reported from Randomized, Vehicle-Controlled Trials

	Amlexanox	Vehicle	No treatment
Application Site Reactions	N = 486	N = 490	N = 178
Pain	36 (7.4)	36 (7.3)	0
Burning	18 (3.7)	15 (3.1)	0
Paresthesia	8 (1.6)	12 (2.4)	0
Irritation	5 (1.0)	6 (1.2)	0
Dryness	0	2 (0.4)	
Reaction NOS	1 (0.2)	14 (2.9)	0
Gastrointestinal Disorders			
Nausea	11 (2.3)	14 (2.9)	0
Mouth Ulceration (i.e., new aphthous ulcers)	8 (1.6)	17 (3.5)	8 (1.7)
Sore Throat NOS	5 (1.0)	6 (1.2)	1 (0.6)
Vomiting NOS	4 (0.8)	1 (0.2)	0
Diarrhea NOS	2 (0.4)	3 (0.6)	0
Nervous System Disorders			
Headache NOS	22 (4.5)	18 (3.7)	2 (1.1)
Taste Disturbance	2 (0.4)	5 (1.0)	0
Fatigue	3 (0.6)	0	0

This table contains data from only the placebo-controlled trials in order to best estimate comparative incidences for common adverse events. Although eliminating the open label safety trial yields a smaller portion of the overall database, the ability to compare rates on drug with a control is an advantage. The subset of trials in the Phase 2 and 3 vehicle-controlled study databases provide the best estimate of incidence rates.

Note that this table presents not only the OraDiscA and its vehicle, but also the no-treatment arm. Although trying to elicit application site reactions when there is no application of either drug or placebo may appear meaningless, note that sore throat and headache were each reported several times. Underreporting of AEs is expected, as subjects who know they are receiving no treatment are less likely to report episodes of headache, nausea, etc. On the other hand, the vehicle group is just as likely as treatment group to report systemic AE's that they experience. None of the common adverse events listed in this table were identified as serious.

The results of this table show a remarkable similarity in reported adverse events between OraDiscA and its vehicle. The only differences in adverse events between the OraDiscA and vehicle are application site reaction NOS and mouth ulceration. Due to the not-otherwise-specified grouping, no further information is available to determine if a more specific type of irritation can be identified. The reported incidence of new aphthous ulcers is much higher in the vehicle than either the OraDiscA group or no treatment group, which may suggest that amlexanox has some sort of preventive effect on new ulcer development. However, the numbers are too small to draw any conclusions.

A revised table that includes all of the studies in which safety was examined will form the basis for the ADR table in labeling in the package insert. That table appears in the next section of this review.

7.1.5.4 Common adverse event tables

The table presented in this section includes not only the vehicle and no-treatment controlled trials, but also the open-label safety study. It is a complete recording of adverse events from all subjects who participated in a trial with the final formulation of OraDiscA. This table includes reactions that occurred at a rate of 1% or more. The application site reactions are likely due to the disk itself, so it is important for the prescriber and patient to see that application site reactions may be expected, but are not worsened by the amlexanox itself. Although the no treatment arm does not add any information to the section on application site reactions, it does give background incidence on the development of new aphthous ulcers, sore throat and headache.

Adverse Events with an Incidence of > 1% - from All Clinical Trials

	Amlexanox	Vehicle	No treatment
Application Site Reactions	N = 409	N = 301	N = 97
Pain	29 (7.1)	25 (8.3)	0
Burning	11 (2.7)	9 (3.0)	0
Irritation	6 (1.5)	6 (2.0)	0
Reaction NOS	5 (1.2)	0 (0)	0
Paresthesia	3 (0.7)	4 (1.3)	0
Gastrointestinal Disorders			
Mouth Ulceration (i.e., new aphthous ulcers)	5 (1.2)	13 (4.3)	6 (6.2)
Nausea	4 (1.0)	5 (1.7)	0
Sore Throat NOS	1 (0.2)	3 (1.0)	1 (1.0)
Investigations			
Liver function tests NOS abnormal	2 (2.0)	Not done	Not done
Nervous System Disorders			
Headache NOS	6 (1.5)	4 (1.3)	0

Note that the additional subjects in this table as compared to the table in section 7.1.5.3 did not significantly change the relationship of adverse events.

7.1.5.5 Identifying common and drug-related adverse events

Application site reactions were the most common AE's and occurred with nearly equal incidence in the treatment and vehicle groups. There were no reports of application site reactions in the no-treatment group, because nothing was applied. It is difficult to determine whether the application site reactions in the amlexanox and vehicle groups are caused by the presence of a disk, or the presence of the aphthous ulcers which may cause

pain, burning, irritation, and paresthesia. However, because the incidence in the amlexanox and vehicle groups is similar it does not appear that the amlexanox itself is contributing to these local reactions to any significant extent.

As the table shows, adverse events in the Gastrointestinal, Investigations and Nervous System SOCs also were reported by at least 1% of patients. Nausea is an event which can result from the taste of the disk, the physical presence of a disk in the mouth, or possibly (but not likely based on the similar numbers of AE reports) from the amlexanox itself. There were no reports of nausea in the no treatment group.

As noted in the previous section, the reported incidence of new aphthous ulcers, (mouth ulceration) is much higher in the vehicle than either the OraDiscA group or no treatment group, which may suggest that amlexanox has some sort of preventive effect on new ulcer development. Sore throat is numerically greater in the active and vehicle groups, but the numbers are small.

Abnormal liver function tests were reported in 2% of the patients in the active arm, and will be discussed in section 7.1.7, laboratory findings.

Headache is much more commonly reported in the active and vehicle groups than in the no treatment group. Bad taste, which occurred with both the test and placebo disk most likely comes from the disk itself and is likely product-related, through not necessarily amlexanox (substance only) related.

To detect significant relationships with hypothesis-testing methods, any reasonable correction for multiplicity would make a "finding" almost impossible and studies are almost invariably underpowered for statistically valid detection of small differences. However, because we cannot rule out the amlexanox or the disk itself as causing any of these events, the Agency concludes that there may be a causal relationship between the OraDiscA and application site reactions, nausea, headache, and sore throat.

7.1.5.6 Additional analyses and explorations

In some cases, it is helpful to perform a more in-depth analysis of adverse events that seem clearly drug-related. For example, exploration for dose dependency, time to onset of AE's, adaptation for common, troublesome events such as somnolence or nausea, demographic interactions, or of drug-disease and drug-drug interactions can be performed. If necessary, selective exploration of individual cases can better characterize the events. In the case of OraDiscA, there is only one dose and one dosing regimen that is used, which rules out this exploration. The lack of severity and relatively low incidence of all adverse events other than application site irritation do not warrant further scrutiny of these AE's. Liver function testing was only performed during the 28-day safety study on subjects using the OraDiscA, so there is no placebo group to compare. The abnormal liver function results were discovered in two subjects of the total users of OraDiscA, and will be examined in further detail in section 7.1.7 to determine if further testing is required.

7.1.6 Less Common Adverse Events

In general, a fairly large database is needed to evaluate less common adverse events. To identify relatively rare events of significant concern, data from the entire Phase 2-3 database as well as data from the open label trial is included. The following listing grouped by system organ class includes adverse events reported with an incidence of between 0% and 0.8%:

Gastrointestinal: Vomiting, diarrhea, abdominal pain, chapped lips, glossodynia, sensitivity of teeth, tongue dry, dry mouth, oral pain, tooth disorder NOS
Skin and subcutaneous tissue disorders: Dermatitis NOS, pruritus NOS
Eye disorders: Eye pain
General disorders: Pyrexia , pain in face
Musculoskeletal, connective tissue and bone disorders: Pain in jaw
Ear and labyrinth disorders: Earache
Respiratory, thoracic and mediastinal disorders: Sneezing

An examination of the numbers and distribution of these AE's between OraDiscA, vehicle, and no-treatment groups in which they appear does not warrant further investigation at this time.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

The studies conducted for efficacy of OraDiscA were of seven-days duration. Laboratory testing was not performed during these studies. In the 28-day open-label study, which was conducted to fulfill long-term safety requirements for approval (AP-C-2U108), laboratory tests as listed below were performed prior to the first application of the amlexanox patch and during the last study visit after 28 days of treatments. Although it is usually preferable to perform the tests on the active and vehicle groups in a clinical trial, the testing of the subjects prior to administration of the drug, and after 28 days of daily use uses the subjects as their own controls to examine any treatment-emergent changes in laboratory values. The labeled duration of use per aphthous ulcer episode is 7 days; by conducting this trial with four back-to-back cycles of treatment, the sponsor has simulated 5-6 months of OraDiscA use. This is adequate, as actual use for recurrent ulcers would have several weeks of no treatment between each cycle of OraDiscA. Any effects on laboratory values should be more readily evident after 28 consecutive days of drug use than with 28 days use extended over six months.

The following laboratory tests were performed:

Hematology: white blood cell (WBC) count with differential, red blood cell (RBC) count, hemoglobin, hematocrit, platelet count.

Serum Chemistry: glucose, sodium, potassium, chloride, blood urea nitrogen (BUN), creatinine, uric acid, phosphorus, serum adjusted calcium, cholesterol, triglycerides, protein, albumin, globulin, alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin, direct bilirubin, lactic dehydrogenase (LDH), bicarbonate, gamma-glutamyl transferase (GGT).

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

Controlled comparisons generally provide the best data for deciding whether there is a signal of an effect of a drug on a laboratory test. Because laboratory testing was performed only in the open label trial, it is not possible to compare any changes from baseline to subjects who received a placebo or no treatment.

7.1.7.3 Standard analyses and explorations of laboratory data

In situations where there is suspicion of a negative impact of the drug on patient laboratory values, three standard approaches to the analysis of laboratory data are often used; the first two analyses are based on comparative trial data, and the third analysis should focus on all patients in the Phase 2-3 experience. Prior exploration of amlexanox's effect on laboratory values in Aphthasol and in amlexanox tablets has not demonstrated any abnormalities. In the case of OraDiscA, there is no comparative data available, as laboratory values were only collected during the uncontrolled open-label study. In section 7.1.7.5, the two subjects who were found to have elevated liver enzymes are discussed to rule out causality of amlexanox to these events. No other laboratory findings required further analyses.

7.1.7.4 Additional analyses and explorations

There is no signal from the summary data to warrant additional analyses for dose dependency, time dependency, or drug-demographic, drug-disease, and drug-drug interactions. Further discussion of the two subjects with treatment-emergent abnormalities in liver function tests, follows in section 7.1.7.5.

7.1.7.5 Special assessments

Two subjects of the 106 who participated in the 28-day open label safety trial of amlexanox patches (study AP-C-2U108) had clinically significant laboratory abnormalities in liver function tests reported. Hepatotoxicity has been an important cause of market withdrawal since the 1950s and deserves a special assessment in this section.

These subjects were measured at the beginning of the trial and at the end. The elevated laboratory values in both subjects were deemed by the investigators to be not related to study medication, but likely due to undiagnosed gallbladder disease and concomitant medication treatment respectively, as described below:

Elevated laboratory values in subject 175-054

Subject #		Normal	Baseline	Day 38
175-054	Alkaline Phosp	37 – 147	169	332
	AST	5 – 45	42	55
	ALT	1 – 55	53	114
	GGTP	1 – 50	123	173

Subject #175-054 had mildly elevated levels of Alkaline Phosphatase and GGTP at screening, which the investigator identified as transient and resulting from ingestion of two tablets of naproxen sodium the evening prior to the screening visit. Although this mild elevation did not exclude the subject from being enrolled, the subject dropped out of the study at Day 3. The subject returned on Day 38 for final laboratory testing and notified the site that a diagnosis of gallbladder stones was made by the subject's physician on Day 59.

Elevated laboratory values in subject 184-064

Subject #		Normal	Baseline	Day 35	Day 45
184-064	Alkaline Phosp	37 – 147	117	165	133
	ALT	1 – 55	18	181	22
	GGTP	1 – 50	17	108	49

Subject 184-064 completed study treatment on Day 31 as planned. On Day 35, alkaline Phosphatase, ALT and GGTP were all elevated. Upon questioning, the subject stated that he had developed a viral infection on Day 32 and was treated with promethazine hydrochloride. On a follow-up visit on Day 45, levels had returned to normal. The investigator concluded that by Day 35, the OraDiscA should not have been responsible for the elevated enzymes, but the temporal association with the promethazine fits the profile. The Agency concurs that amlexanox is not likely to have been the cause of the transient elevation.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs were measured at baseline only during the 28-day safety study for the purposes of determining eligibility for the study. There was no vital sign assessment during the phase 3 trial. Therefore, no analyses were conducted on vital signs or physical findings. Based upon the prior approval of Aphthasol paste, 16-year systemic use of amlexanox in Europe at 10 – 20 times the dose, and the minimal absorption of amlexanox, vital sign monitoring during the trial was not deemed to be necessary.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

No overall drug-control comparisons were made. As is noted in 7.1.8.1, vital signs were only measured at baseline to determine eligibility for enrollment.

7.1.8.3 Standard analyses and explorations of vital signs data

No standard analyses and explorations of vital signs data were performed. As is noted in 7.1.8.1, vital signs were only measured at baseline to determine eligibility for enrollment.

7.1.8.4 Additional analyses and explorations

No additional analyses of vital signs data were performed. As is noted in 7.1.8.1, vital signs were only measured at baseline to determine eligibility for enrollment.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

There were no ECGs obtained during any of the studies, either at baseline or during the course of the study. This drug is a topical drug that demonstrates virtually no systemic absorption through the oral mucosa. The only systemic exposure is through swallowing the disk as it slowly dissolves. Based upon the prior approval of Aphthasol cream, which resulted in swallowing the same amount of active ingredient, as well as a 16-year history of systemic use of Amlexanox in Europe at 10 – 20 times the dose for a chronic indication, its cardiac safety has been well established.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

No overall drug-control comparisons were made. As is noted in 7.1.9.1, ECG testing was not performed.

7.1.9.3 Standard analyses and explorations of ECG data

No standard analyses and explorations of ECG testing were performed. As is noted in 7.1.9.1, ECG testing was not performed.

7.1.9.4 Additional analyses and explorations

No additional analyses of ECG data were performed. As is noted in 7.1.9.1, ECG testing was not performed.

7.1.10 Immunogenicity

Although amlexanox has been shown to have antiallergenic activity in various models of Type I to Type IV allergic reactions when provided by systemic administration, many cases of contact dermatitis have been reported with certain of the topical forms of amlexanox. In Japan, there is a marketed ophthalmic solution containing 0.25% amlexanox. Of the — million patients who used amlexanox ophthalmic solutions, 125 cases of contact dermatitis associated with the ophthalmic solution were reported to the manufacturer. The dermatitis occurred primarily around the eyes and it was concluded that amlexanox was a sensitizer when brought into direct contact with the skin around the eyes. Similarly, one study with a 1% gel formulation of Amlexanox being tested in

patients with oral lichen planus has resulted in a high degree of sensitization, and skin testing suggested an immune-mediated hypersensitivity reaction. Repeated patch-application tests conducted with an investigation of a 2.5% and 5.0% cream formulation also resulted in a high degree of hypersensitivity.

Therefore, prior to approval of amlexanox paste in the U.S., a repeated-injury patch test study was conducted in 200 healthy volunteers. In addition, a long-term safety study was conducted in 100 patients with aphthous ulcers for 28 days. No sensitization reactions were observed in either study. Post-marketing surveillance of Aphthasol in the U.S. has included only 16 reports of allergic reactions to the oral cavity or face between 1995 and 2001. During that period of time, [ ] tubes of Aphthasol were dispensed. In addition, the oral amlexanox tablets in Japan have reported very few skin eruptions, leading to speculation that systemic administration of amlexanox results in a low incidence of sensitization.

In conclusion, the allergenicity of amlexanox appears to be primarily a function of the formulation – Amlexanox oral tablets, amlexanox 5% paste, and amlexanox 2 mg oral patches have a low incidence of hypersensitivity reactions, whereas ophthalmic solutions, creams and gels have a much higher incidence of hypersensitivity. Since the potential exists for cases of hypersensitivity with OraDiscA once in widespread use, a statement about discontinuing use if hypersensitivity develops is warranted.

7.1.11 Human Carcinogenicity

No human carcinogenicity studies were conducted under the IND for OraDiscA or Aphthasol. There were no data or literature submitted to this NDA on the topic.

7.1.12 Special Safety Studies

In some cases, special studies are warranted for concerns that arise such as QT interval abnormalities, or drugs that are intended to demonstrating a safety advantage over other therapies. Although this is not the case for OraDiscA, one safety concern unique to a mucoadhesive patch that the sponsor addressed was the risk of aspiration, since the patch is applied to the oral mucosa and designed to dissolve slowly over time. In fact, one of the reasons that the sponsor changed formulations between Phase 2 and Phase 3 of development was to eliminate a [ ] backing and substitute a cellulose-based one. The sponsor was concerned that if some patients did not understand that the [ ] backing was to be removed before placement, there would be a danger of swallowing or aspirating the [ ] The sponsor addressed the concern about aspiration in two ways. They monitored the clinical trials of 603 subjects using OraDiscA as well as an additional 409 subjects using a vehicle patch, and found no reports of accidental aspiration or detrimental swallowing of the patches. In addition, the sponsor conducted a pharmacokinetics study in which the erosion time of the patch was specifically measured and the subjects queried about particulate dissolution. The patch eroded within 1 – 2 hours, and subjects did not have problems with the OraDiscA breaking into large particles. In spite of the apparent safety in these clinical trials, the sponsor decided to

include in the label a statement advising patients against using the disk too close to bedtime to prevent aspiration while sleeping.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Amlexanox paste has been used for the same indication in the US for seven years, and amlexanox has been taken internally in Japan since 1987 for allergic rhinitis. There have been no signals of abuse potential or withdrawal symptoms. Therefore, no studies were designed to assess these issues. No concerns about abuse potential have arisen from the studies conducted for this NDA. The Agency concurs that there is no need to examine this area any further at this time.

7.1.14 Human Reproduction and Pregnancy Data

No formal studies in humans of the effects of drugs on reproduction or pregnancy were performed. Similarly, no information on drug exposure in pregnant women, including any inadvertent exposure during drug development was identified. Teratology studies were performed with rats and rabbits at doses up to two hundred and six hundred times, respectively, the projected human daily dose, on a mg/m^2 basis. No adverse fetal effects were observed. At doses up to two hundred times the projected human daily dose, on a mg/m^2 basis, amlexanox did not have a significant effect on peri- or postnatal development of rat fetuses. Because animal reproductive studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. Therefore, OraDiscA is recommended for Pregnancy Category B.

7.1.15 Assessment of Effect on Growth

This drug was tested in children age 12 and older and is labeled as such. The efficacy trials were of seven-days duration, and the long-term safety study was 28 days. There was no concern either prior to the conduct of these clinical trials or during the review of this NDA that topical amlexanox has an effect on growth or development. Data were not collected to examine this parameter.

7.1.16 Overdose Experience

There are no reports of overdosage. Ingestion of 20 patches (proposed packaging for one prescription) would result in systemic exposure well below the maximum nontoxic dose of amlexanox in animals, as well as below the maximum daily oral dose of 50 mg of amlexanox tablets t.i.d. used to treat asthma in other parts of the World. Gastrointestinal upset such as nausea, vomiting, and diarrhea could result from an overdose.

7.1.17 Postmarketing Experience

OraDiscA has not been marketed in the U.S. or any other country. However, amlexanox has been marketed in the U.S. since 1996 as Aphthasol 5% paste, and has been marketed in Japan as 50-mg oral tablets. Examination of postmarketing experience for both of these is helpful for a complete review of OraDiscA.

The post-marketing experience with Aphthasol in the U.S. has included reports of 16 cases that can potentially be characterized as hypersensitivity reactions (oral cavity or face) between October 1995 and June 2001. A total of [ ] tubes of Aphthasol were sold by pharmacists during that time period. Amlexanox tablets have been marketed in Japan since 1987 and postmarketing surveys have included reports of dermal effects such as rashes, urticaria and pruritus; central nervous system effect such as headaches, dizziness, sleepiness and insomnia; gastrointestinal effects such as vomiting, nausea, and diarrhea, and increased liver enzymes. The reported abnormalities of liver function testing occurred in patients receiving chronic doses of amlexanox at 75 – 150 mg/day for 15 – 84 days of treatment. The changes were asymptomatic and returned to normal levels following discontinuation of treatment. The incidence of elevated liver enzymes occurred in 0.2% of patients who were tested in the post-marketing surveys of amlexanox tablets.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

The table of clinical studies that appears in Section 4.2 summarizes the clinical trials that were submitted to this NDA to support both safety and efficacy. Although only three of them contained data that was used in the evaluation of efficacy, all of these trials collected safety data which were evaluated for the purposes of establishing safety of OraDiscA. The phase 2/3 and phase 3 pivotal trials examined 460 subjects using OraDiscA for seven days and the open label study evaluated 106 subjects using OraDiscA for 28 days. As was discussed in Section 6.1.4, there was adequate representation of individuals from the major U.S. racial groups, men and women, and all age groups over 12.

7.2.1.1 Study type and design/patient enumeration

Refer to Section 4.2 for the table that lists all clinical trials and summarizes the design features and number of subjects in each trial. The subjects included in the safety evaluation were enrolled in five clinical trials. Three of the trials were vehicle-controlled, efficacy and safety trials, based on seven days of treatment or less, and four-times-daily applications. This corresponds to treatment during a single episode of an aphthous ulcer. In the fourth study, the safety of repeat treatment with OraDiscA was evaluated using 106 subjects with aphthous ulcers. The subjects were enrolled in the long-term safety clinical trials and asked to treat one or two ulcers with OraDiscA four times a day for 28 consecutive days. The sponsor did this to simulate exposure that is equivalent to four to five consecutive treatment courses. The fifth study was a phase 1 pharmacokinetics study in healthy individuals that primarily determined if there were any early signs of safety problems before enrolling aphthous ulcer patients.

The 28-day safety trial and the pivotal seven-day safety and efficacy trials were conducted with the final formulation of OraDiscA, whereas the other two trials were conducted with the earlier formulation. As has been discussed earlier in this review, although there were some concerns about how the change in formulation might affect the efficacy results, the safety data from the two formulations should be comparable.

A total of 409 subjects with aphthous ulcers were exposed to the final formulation and 309 to its vehicle patch. An additional 194 subjects with aphthous ulcers were exposed to the earlier formulation and 189 to the vehicle formulation of the earlier formulation. Therefore, the total number of subjects included in the safety database is 603 (409 + 194) subjects on active amlexanox patch.

7.2.1.2 Demographics

Refer to the table in Section 6.1.4 which contains the demographic breakdown of subjects. In all studies, significantly more female than male subjects were enrolled with an almost 2:1 ratio. The relative proportion of women versus men among studies and treatment-groups ranged from 73% vs. 27% (vehicle group in AP-C-9E02) to 57% vs. 43% (vehicle group in AP-C-9E03). This gender difference is due to the fact that more women are affected by recurrent minor ulcers plus women in general are more likely to volunteer for clinical trials. In spite of the higher percentage of female enrollees, there are sufficient men to examine gender differences in safety or efficacy. In terms of racial enrollment, it must be noted that the percentage of Caucasians (86%) is slightly higher than in the overall U.S. population and the African-American population is slightly lower than in the overall U.S. population. (2000 Census – 83% Caucasian, 13% Black, 9% Hispanic). Although there were too few enrollees from minority races to perform statistical testing, those subjects were examined for trends in both safety and efficacy evaluations. The mean age for subjects enrolled in the pivotal trial (29.7 years) is lower than the US population (35.8 years). Subjects were enrolled from the age of 12 with no upper limit. Due to a lack of formal recruiting of geriatric patients, their numbers were very small, and although no conclusions could be made, the safety and efficacy were similar in trend to the other adults.

7.2.1.3 Extent of exposure (dose/duration)

There was only one dosing regimen used for all trials – one patch four times per day. Because this dosing was established in the Aphthasol product, the sponsor did not wish to explore other strengths or dosing frequency. For the purposes of testing, a seven-day dosing, which is the same dosage and administration as proposed for the label, was used in all of the trials with the exception of the open label trial. That trial was conducted for 28 days, which approximates four cycles of treatment to simulate chronic use.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

Secondary source data are (1) data derived from studies not conducted under the applicant's IND and for which CRFs and full study reports are not available, or studies so poorly conducted (e.g., poor ascertainment for adverse events) that they cannot be reasonably included in the Primary Source Database, (2) postmarketing data, and (3) literature reports on studies not conducted under the IND. As has been described in Section 7.1.17 of this review, amlexanox has been marketed in the U.S. since 1997 as Aphthasol 5% paste, and is marketed in Japan as 50-mg oral tablets.

Because Aphthasol was approved under an NDA, reporting of post-marketing experience is mandated and all reports have been reviewed. A total of [ ] tubes of Aphthasol were sold during that time period, which suggests significant exposure. Amlexanox tablets have been marketed in Japan since 1987 and in addition to spontaneous reporting, formal postmarketing surveys have been conducted. Because of chronic doses of 75 – 150 mg amlexanox/day, liver enzyme activity, in particular, was monitored.

7.2.2.2 Postmarketing experience

Although OraDiscA has never been marketed either in the United States or elsewhere, other amlexanox-containing products including Aphthasol and amlexanox 50-mg tablets have. Postmarketing data for Aphthasol are available through the FDA's Adverse Events Reporting System (AERS), and have been evaluated and included in the relevant sections of this review. Data and published literature regarding the amlexanox tablets, which are not marketed in the United States, are not as widely available, but have also been included in the pertinent sections of this review. Important events from these other products have been described in appropriate sections (e.g., 7.1.1 and 7.1.2, Deaths and Other Serious Events; 7.1.16, Overdose Experience).

7.2.2.3 Literature

Most of the literature submitted to this NDA consists of published toxicology studies and papers discussing the etiology and epidemiology of recurrent aphthous ulcers. In terms of referencing studies on other forms of amlexanox, the sponsor owns the data from Aphthasol, so instead of published literature, the actual study reports and tables were provided.

For completeness, literature searches were conducted by the reviewer to ascertain that no published reports that might raise safety or efficacy issues were omitted from the NDA.

7.2.3 Adequacy of Overall Clinical Experience

A total of 592 subjects were exposed to OraDiscA in all studies. Of these, 493 completed studies in which they used OraDiscA for seven days and 99 subjects completed studies in which they used OraDiscA for 28 days. The trials which were of seven days duration tested the drug for the recommended duration of application for each aphthous ulcer

incident. Only the open-label safety study was long enough to simulate six months of chronic use experience. Since many aphthous ulcer sufferers develop ulcers on a fairly regular basis, it is not unusual to be treated for a seven-day cycle 10-12 times per year. This qualifies as a chronic use drug. As recommend by the ICH guidance on extent and duration of exposure, long-term safety data should be collected on a sufficient number of subjects for a sufficient duration to assess safety for chronic use drugs. In the open-label trial, 99 subjects completed the 28-day study. As will be discussed further in Section 7.2.8, this smaller than recommended number must be balanced against the very positive safety profile gathered from the open-label use study as well as the profile from the 493 subjects using OraDiscA in the normal seven-day cycle, 303 of whom received OraDiscA in the pivotal trial. In addition to that, the sponsor has submitted all safety data from Aphthasol, which contains the same amount of amlexanox as OraDiscA and is approved for chronic use.

Adequate representation of men and women, individuals of Caucasian, African American and Hispanic background, and adolescents from 12 – 17 were represented. Patients who were excluded from the study such as diabetics and tobacco users, do not limit the relevance of safety assessment, although their exclusion does leave concerns about generalizability of efficacy and are addressed in the proposed labeling. There were no class effects evaluated, other than potential for local irritation from the class of topical drug products. Refer to Section 8.4 for a full discussion of the adequacy of pediatric enrollment and outcome.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Given the preclinical program conducted prior to Aphthasol's approval and the seven years of human experience for Aphthasol, no additional preclinical testing or in vitro testing was necessary.

7.2.5 Adequacy of Routine Clinical Testing

The routine clinical testing of study subjects presented in this submission, including efforts to monitor laboratory parameters, vital signs, and efforts to elicit adverse event data is adequate. Because of the extensive safety testing of amlexanox during the approval process for Aphthasol, it was not necessary to repeat most of this testing for OraDiscA. Vital signs and ECG data were not collected during the clinical trials, but there was no reason to require this for a topical drug with a safe history. Laboratory parameters were monitored during one of the trials at baseline and during the final visit. Although there was no control group for comparison, the subjects were compared to their baseline values. There were very few shifts in lab values, and for those few, no cause for concern for patient safety was identified. The adequacy of specific testing intended to assess certain expected or observed events is discussed under subheading 7.2.7.

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

Section 5 of this review summarizes the clinical pharmacology for amlexanox. Although the exact mechanism of action of the drug is unknown, metabolism and excretion is

sufficiently understood to ease concern about safety problems in patients with impaired excretory or metabolic function, as well as problems resulting from drug-drug interactions.

Both in vitro and in vivo testing carried out by the sponsor were adequate to identify the following: 1) the enzymatic pathways responsible for clearance of the drug and the effects of inhibition of those pathways, notably CYP450 enzymes and p-glycoproteins 2) the effect of the drug on CYP450 enzymes (inhibition, induction) and the effects of the drug on the PK of model compounds and 3) the major potential safety consequences of drug-drug interactions. None of these issues raised concerns that require further testing or specific labeling for OraDiscA.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

The sponsor has adequately gathered information, reviewed data from related products, and analyzed information to detect specific adverse events that are potentially problematic and might be expected with a drug of any class (e.g., QT prolongation or hepatotoxicity) or that are predicted on the basis of the drug class. Because of a concern about potential sensitization, the sponsor conducted additional testing, and because of the sponsor's concern about aspiration of the disk, additional testing was conducted and specific labeling recommended.

7.2.8 Assessment of Quality and Completeness of Data

The quality and completeness of the data submitted for conducting the safety review were sufficient to make the judgment that OraDiscA is safe to proceed to market. As has been discussed throughout the safety portion of this review, information obtained from earlier formulations of amlexanox was used as evidence of safety for the drug substance, amlexanox. Adequate analysis and interpretation of the safety results, including laboratory values, adverse event reporting, and pharmacokinetics have made for a thorough examination of OraDiscA.

Fewer than the ideal number of subjects (100) were enrolled to test chronic use of the drug. This smaller than ideal number is balanced against the very positive safety profile gathered from the chronic use study as well as the safety profile from the 500 subjects on Amlexanox in the normal seven-day cycle. In addition, the sponsor has submitted all safety data from Aphthasol, which contains the same amount of amlexanox as OraDiscA and is approved for chronic use. Given that nothing surfaced as a potential safety issue from the wide range of safety data that were submitted, the totality of the safety evidence is sufficient to support the conclusion that OraDiscA is safe.

7.2.9 Additional Submissions, Including Safety Update

The only additional safety submission to this NDA after the initial submission was the 4-month safety update, which was received on August 23, 2004. Since no clinical trials

have been preformed between December 2003 when the original NDA was submitted and July 30, 2004, there is no additional clinical trial safety information to report regarding the OraDiscA drug product. However, the report of a clinical pharmacology safety study is included in this update, which was conducted to evaluate the effects of amlexanox on CYP450 19, 1A2, 2C19, 2D6 and 3A4 and amlexanox binding to the hERG potassium channel protein. The conclusion is that amlexanox did not significantly affect any of the six cytochrome P450 enzymes tested in this study, or the hERG potassium channel. This information is presented in the Clinical Pharmacology section of this review (Section 5).

There are no reports of important changes in Aphthasol labeling or foreign labeling.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

The only adverse events that are potentially treatment-related are local irritation at the placement site of the OraDiscA, and possibly nausea, sore throat and headache. The incidence of these events is fairly low at the highest being pain at 7%. Background pain from an aphthous ulcer was not measured, but is likely to be at least that high as well. None of the events reported were serious in nature. Inclusion in the label of a chart that provides this information is sufficient.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

Safety data were examined both on an individual study basis and as pooled data, depending upon the intent of the data review. In order to estimate the incidence of adverse events in clinical trials, the data were first tabulated, using only the controlled clinical trials. The subjects were blinded and therefore, a comparison to vehicle provides a fairly realistic picture of how much of an adverse effect is related to the study medication. The use of an open label study or other unblinded or uncontrolled trials could bias the results.

On the other hand, pooling all of the safety data increases the sample size and increases the chance of seeing lower frequency events, which can be difficult to detect and may not occur in some studies. Pooling can also provide a larger database that will permit explorations of possible drug-demographic or drug-disease interactions in population subgroups. In the safety review, the source of the data has been identified in each section.

7.4.1.2 Combining data

As described in 7.4.1.1, safety data were pooled to increase the likelihood of uncovering adverse events that occur with a low frequency. The pooling procedure consisted of

combining the numerator events and denominators for the selected studies. Although more formal weighting methods can be used (e.g., weighting studies on the basis of study size or inversely to their variance), this was not deemed necessary for OraDiscA.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

There is only one dose of OraDiscA proposed.

7.4.2.2 Explorations for time dependency for adverse findings

The recommended use for OraDiscA is seven days for each aphthous ulcer occurrence. All of the clinical trials except for the open-label trial were of seven days duration. The open-label study of 28 consecutive days had a slightly higher incidence of adverse events, which is expected due to the much greater exposure time. Since the dosing for each aphthous ulcer outbreak is seven days, the results from the seven-day studies are more typical of actual use. Nonetheless, the 28-day safety data is included in the pooled safety data results.

7.4.2.3 Explorations for drug-demographic interactions

The effectiveness and safety of OraDiscA was explored to the extent possible in race, age, and gender subgroups. Although there is some concern about effectiveness in children between the ages of 12 and 17, there were no safety concerns in any of these groups.

7.4.2.4 Explorations for drug-disease interactions

There was no evidence of drug-disease interaction.

7.4.2.5 Explorations for drug-drug interactions

There was no evidence of drug-drug interaction.

7.4.3 Causality Determination

Although determining an association of certain safety events with a drug is straightforward, establishing causality is not. Causality generally requires not only an association, but strength of association, temporal match, and biological plausibility. A test often employed is withdrawing the drug and observing whether the associated event abates; rechallenging the subject with the drug should then reinitiate the event in a causal relationship.

The mission of the Agency is to allow only safe and effective drugs to market. Given that causality is difficult to prove, if the Agency has reason to believe that a particular AE is likely to be caused by a drug, the Agency has an obligation to limit the potential harm of this drug.

Fortunately, in the case of OraDiscA, none of the reported AEs were serious and none occurred with a high incidence. In terms of whether the associated AEs such as local irritation, nausea, sore throat, or dizziness are causally related, the best answer is possibly or likely. The most numerous AE, local irritation, is nearly equal between OraDiscA and its vehicle. Because of this, the most likely scenario is that the physical presence of the disk may be causing these local irritations. However because the no-treatment group did was not asked about local irritation from the disk (since there was no disk), there is no comparison to the background local irritation caused by the ulcer itself. A better way to have evaluated the response would have been also asking the no-treatment group about irritation at the aphthous ulcer site in a way that was similar to asking the OraDiscA and vehicle groups.

In terms of the other events such as nausea, sore throat and headache, there were some responses in the no-treatment group, but the lack of blinding certainly biases the response towards a lack of reports. For these events, it is probably most conservative to consider them all possibly or likely related to the study drug.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The 2-mg patch of amlexanox is the only dose of OraDiscA proposed, and the dosing regimen is one patch placed on the area affected by the aphthous ulcer four times per day. Although most individuals only experience one aphthous ulcer at a time, for those who experience multiple concurrent aphthous ulcers, the drug is proposed to be used to treat up to three ulcers at one time, with one OraDiscA placed on each ulcer.

The dose chosen for OraDiscA was identical to the dose for Aphthasol. The 2 mg of amlexanox in each OraDiscA corresponds to the approximate amount of amlexanox in one dab of 5% amlexanox paste, which is currently marketed in the United States. The proposed frequency of four times per day is also identical to the frequency that was proved efficacious for the amlexanox paste; the sponsor suggests that this is the highest frequency of administration with which patients are likely to comply. It would have been ideal to experiment with lower doses since it was expected that this OraDiscA new delivery system would be more efficient than the paste at supplying the same amount of amlexanox to the site and retaining it there longer. Nonetheless, amlexanox was shown in Aphthasol to have a very safe profile, and the Agency had no comments during the IND phase of development about exploring other dosing.

8.2 Drug-Drug Interactions

No drug-drug interactions were uncovered during the review process; based upon testing results, amlexanox is unlikely to have an effect on drugs or xenobiotics metabolized by cytochrome P450. There are no recommendations for dosing adjustments.

8.3 Special Populations

No formal studies in humans of the effects of drugs on reproduction or pregnancy were performed; similarly, no information on drug exposure in pregnant women, including any inadvertent exposure during drug development, was identified. The drug is recommended for pregnancy category B through review of reproduction studies which have been performed in rats and rabbits at doses up to 300 mg/kg/day (approximately 70 and 145 times the maximum human dose in rats and rabbits, respectively, when comparing on the basis of body surface area estimates). Those studies revealed no evidence of impaired fertility or harm to the fetus due to amlexanox. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Patients with hepatic and renal insufficiency are not restricted in their use of OraDiscA.

In the pivotal trial, patients who were diabetic or tobacco users were excluded from the trial. The sponsor eliminated diabetics because they did not want the confounding of potential wound healing difficulties; however, it is not clear why smokers were eliminated. Literature suggests a lower incidence in tobacco users than in non-smokers, so it is possible that the sponsor wanted an enriched population by eliminating them. However, with such a high prevalence of smokers in the United States, the studies have eliminated the study of OraDiscA in a large segment of the target population. The sponsor's proposed labeling will be modified to reflect the uncertainty about the effect of OraDiscA on smokers. The exclusion of diabetics should be mentioned in the clinical trials description of the label.

8.4 Pediatrics

The Agency granted a partial waiver of pediatric testing to children under the age of 12. Although children younger than 12 do get aphthous ulcers, the Agency concluded that given that the disk size may pose a safety concern in young children and the need to comply with four times per day dosing, OraDiscA would not be appropriate for individuals under the age of 12.

Patients between the ages of 12 and 17 participated in the OraDiscA studies with a total enrollment of 79 subjects in groups using OraDiscA, 60 subjects assigned to the vehicle disc, and 16 who were in the no-treatment group. Of the 79 subjects on OraDiscA, 25 were in the open label study and experienced 28 consecutive days of exposure; the remaining 51 were in seven-day trials.

The safety data from the clinical trials provides sufficient evidence of OraDiscA's safety in the pediatric population down to the age of 12. The incidence of adverse events affecting the application site was similar for the amlexanox patch and vehicle patch treatment groups. For the pediatric subjects receiving OraDiscA, 3% of these subjects on

OraDiscA reported pain at the application site, compared to 2% in the vehicle group; 3% reported paresthesia in both the OraDiscA and vehicle groups; and 3% of subjects reported headache in the OraDiscA and vehicle group. None of these subjects withdrew due to an adverse event, and none of the events were significant.

Efficacy of OraDiscA was examined in children between the ages of 12 and 17. Although the safety data were adequate to conclude that it is safe for use in children of this age, the sample size was too small in this age group to be conclusive about the efficacy data in children. There is no biological hypothesis or supporting evidence that children would respond differently to amlexanox than adults. However, pediatric trials are always challenging, particularly in cases where compliance is an issue such as this one where the children would need to be placing new disks four times a day for 7 days.

Based upon the strong safety profile of OraDiscA and the lack of literature to suggest that aphthous ulcers in adolescents behave differently than in adults, there is no reason to request further testing in adolescents. In the pediatric section of the label, the information gathered from the clinical trials should be accurately presented, including an adequate demonstration of safety, and the inability to specifically report efficacy in pediatric patients.

8.5 Advisory Committee Meeting

There were no advisory committee meetings in which OraDiscA or any other drug product containing amlexanox was discussed.

8.6 Literature Review

Literature related to the application has been referenced throughout the review as needed. As was discussed in Section 7.2.2.3, most of the literature submitted to this NDA consists of published toxicology studies and papers discussing the etiology and epidemiology of recurrent aphthous ulcers. There is no need for a separate comprehensive review of the literature.

8.7 Postmarketing Risk Management Plan

There is not a need for a postmarketing risk management plan.

8.8 Other Relevant Materials

There are no other relevant materials that are not included in other sections of the review. The results of a review of the product name from the Division of Medication Errors and Technical Support (DMETS) in the Office of Drug Safety (ODS) is discussed in Section 9.4 of this review.

9 OVERALL ASSESSMENT

9.1 Conclusions

OraDiscA patch (2 mg amlexanox in a patch) has shown adequate evidence of effectively improving the healing of aphthous ulcers. In one placebo-controlled, randomized and blinded clinical trial of seven days duration, a significantly higher percentage of aphthous ulcer patients experienced complete healing on Day 5 of OraDiscA treatment compared to those who were supplied with a vehicle disk. Data from a non-pivotal phase 3 trial were also used to reinforce the pivotal trial efficacy results. OraDiscA has been shown to be safe for its intended use as recommended in the labeling by all tests reasonably applicable to the assessment of safety. These include comparison of adverse events in the clinical trials between groups, reviewing laboratory data, reviewing postmarketing reports from already marketed amlexanox products, and gathering chronic use data from an open label safety trial. Demographic data allowed evaluation of safety and efficacy in subgroups based upon race and gender. Sufficient data have been submitted and reviewed to provide adequate directions for use, including data that describe a safe and effective dose.

The efficacy results in the 12 – 17 year old pediatric population are inconclusive due to a sample size that is too small for adequate analysis. However, safety was adequately demonstrated, and there is no biological explanation for any difference between the effect in adults and in adolescents.

9.2 Recommendation on Regulatory Action

This new drug application is recommended for approval. The efficacy has been demonstrated through one well-controlled pivotal study. Data gathered was adequate to assess safety, and included not only adverse event monitoring during the trials, but also pre-marketing and postmarketing evaluations for Aphthasol and postmarketing data that was available for oral amlexanox. No Phase 4 commitments will be requested. The sponsor's proposed labeling as submitted in the NDA requires revision before approval.

9.3 Recommendation on Postmarketing Actions

There are no recommendations for postmarketing actions.

9.3.1 Risk Management Activity

There are no recommended postmarketing risk management activities.

9.3.2 Required Phase 4 Commitments

There are no required Phase 4 commitments.

9.3.3 Other Phase 4 Requests

There are no other Phase 4 requests.

9.4 Labeling Review

A review from the Division of Medication Errors and Technical Support (DMETS) in the Office of Drug Safety (ODS) was completed and sent to the OraDiscA reviewers in the review Division on August 13, 2004. DMETS does not recommend the use of the proprietary name OraDisc™ A due to the possibility of look-alike and sound-alike confusion with Orudis KT, Oralone, Orabase HCA, and Oraqix. On August 16, 2004, the sponsor received these comments via facsimile transmission. There has been no proposal for developing a Medication Guide or Patient Package Insert for OraDiscA.

The appendix to this review includes a line-by-line review of the proposed label, with appropriate markings for every suggested addition and deletion to that text. In the remainder of this section, a summary of the major changes needed in the sponsor's proposed labeling is presented. Refer to the appendix for a line-by-line review.

The major changes to the sponsor's proposed label that the Agency recommends include the removal of the description and results of the non-pivotal trial, the addition of tables in the clinical studies and adverse events section of the label. The storage conditions also need revision per the CMC reviewer.

In the Clinical Studies section, the sponsor had proposed language to describe the results of both the pivotal phase 3 study and a non-pivotal phase 2/3 study. As has been discussed in this review, the non-pivotal study was only used to clarify certain results from the pivotal trial, but due to the formulation difference, not be cited as pivotal. Therefore, the description and results from that nonpivotal trial are eliminated from the label. For the description of the pivotal trial, the sponsor only discussed the results for healing and pain relief at Day 5, which does not provide a balanced assessment of what patients could expect during the entire seven days. Substitution of two tables - one for the healing and one for pain relief that provide a complete and easy-to-read synopsis is preferable. Similarly, the sponsor provides a brief narrative of the adverse reactions observed in the trial. However, a table that shows the distribution of the events in all three arms provides much more information and has been added to the narrative. Because the CMC review determined that 12-month stability was not demonstrated at [ ] the labeling should be changed to reflect the acceptable alternative, 25° C.

9.5 Comments to Applicant

After completing internal team discussion of the sponsor's proposed label, the Agency sent comments from DMETS as well as the review division. These have been incorporated into the label that follows.

10 APPENDICES

10.1 Review of Individual Study Reports

Highlights of the individual studies were discussed in the body of this review. No further review of individual study reports is warranted.

10.2 Line-by-Line Labeling Review

In this section, three sets of the label will be provided. The first label is the sponsor's proposed label (Section 10.2.1). The second label is the Division-revised label (Section 10.2.2).

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_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

6 Page(s) Withheld

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_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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/s/

Fred Hyman
9/24/04 12:52:03 PM
MEDICAL OFFICER

John Kelsey
9/24/04 03:50:00 PM
MEDICAL OFFICER
See Multi-disciplinary Summary which clarifies the extent to which approval is based upon data from studies using the early formulation of the product.

Jonathan Wilkin
9/24/04 04:27:17 PM
MEDICAL OFFICER
See TL Multidisciplinary summary

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-727

Chemistry Review(s)

NDA 21-727

Tradename
(2mg Amlexanox, Mucoadhesive Patch)

Access Pharmaceuticals, Inc.

Ernest G. Pappas

Division of Dermatological and Dental Drug Products

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II. **Review Of Common Technical Document-Quality (Ctd-Q) Module** **22**

A. Labeling & Package Insert **22**

B. Environmental Assessment Or Claim Of Categorical Exclusion **22**

III. List Of Deficiencies To Be Communicated **22**

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Chemistry Review Data Sheet

1. NDA 21-727

2. REVIEW #: 1

3. REVIEW DATE: 9/20/04

4. REVIEWER: Ernest G. Pappas

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
NA	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	12/4/03
Amendment	2/2704
Amendment	3/15/04
Amendment	8/30/04
Amendment	9/20/04

Note: Amendment dated 3/15/04 indicated that FDA's request of 2/0/04 regarding questions raised via Filing Review Letter was answered with the 3/15/04 amendment (see below).

7. NAME & ADDRESS OF APPLICANT:

Name:	Access Pharmaceuticals, Inc.
Address:	2600 Stemmons Freeway, Suite 176 Dallas, TX 75207-2107
Representative:	David P. Nowotnik, Ph.D; Senior VP Research

Telephone: (214) 905-5100

8. DRUG PRODUCT NAME/CODE/TYPE: Amlexanox; AA-673

a) Proprietary Name: OraDisc™ A
b) Non-Proprietary Name (USAN): Amlexanox 2 mg, Mucoadhesive Patch
c) Code Name/# (ONDC only)
d) Chem. Type/Submission Priority (ONDC only):
- ☐ Chem. Type: 3
- ☐ Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b) (1)

10. PHARMACOL. CATEGORY: Treatment of Aphthous Ulcers

11. DOSAGE FORM: Mucoadhesive Patch

12. STRENGTH/POTENCY: 2 mg

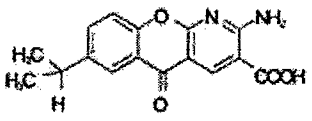
13. ROUTE OF ADMINISTRATION: Topical

14. Rx/OTC DISPENSED: x Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT: 298.30



Amlexanox

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	IV	[redacted]	[redacted]	7	Never reviewed	Not required	USP monograph.
[redacted]	IV	[redacted]		7	Never reviewed	Not required	USP monograph
[redacted]	III	[redacted]		3	Acceptable		Reviewed 4/12/02

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
n/a		

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
EES			
LNC (DMETS)	Tradename(***OraDisc*™ *A***) not acceptable; all other acceptable.	7/19/04	Kristina Arnwine
Methods Validation	Not acceptable; MV package inadequate.	As of 8/27/04	
Microbiology	Acceptable	9/17/04	Bryan Riley

19. ORDER OF REVIEW (OGD Only) NA

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 21-727

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA can be approved from a Chemistry standpoint. However, there are some minor CMC and labeling issues that need resolution by the applicant.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Amlexanox 2 mg, Mucoadhesive Patch, packaged in units of 20 patches in a sealed HDPE bottle, with a [redacted] cap with foil seal.

This patch is made up of four layers; a mucoadhesive layer that is to come in contact with the mucosal tissue the, a binding layer, a polymer film layer, and a coating layer. This film has the following configuration:

Diagram of Formula

The drug substance is the same API that was approved for Aphthasol ®, Amlexanox Oral Paste 5% (NDA 20-511) for the treatment of aphthous ulcers in the mouth.

There are [redacted] that were observed in the manufacture of Amlexanox 2 mg, Mucoadhesive Patch. They are as follows:

[ ]

[

] In this regard, in-process controls [

], are performed to assure [

] In addition, the release specifications give added assurance of the identity, strength, quality and purity for the finished product.

The applicant proposed a tentative expiration date of 12 month when stored at 25 ^{0}C (Control Room Temperature). Acceptable stability data were submitted to support ambient storage conditions (25 ± 2 ^{0} C/ 60% RH). However, the stability data failed dissolution testing at accelerated [ ], after [ ], and intermediate conditions [ ] and [ ] respectively. The firm indicated that, after evaluating the properties [ ] Amlexanox at temperatures above 25 ^{0}C . A 12 month expiration date has been granted for the drug product.

The tradename, OraDisc ™ has been found not acceptable by DMETS. This reviewer agrees with DMETS because of the " Look-Alike/Sound-Alike Issues" to the marketed product "Orudis KT". Also, the label should reflect a storage statement of 25^{0}C with a Caution statement "Do Not Store above 30^0 C".

Establishment Inspection: An overall recommendation of "Approvable" were given for the four facilities from the Office of Compliance as of 9/14/04 (see pg. 77 below).

Environmental Assessment: The applicant claims a categorical exclusion from the preparation of an Environmental Assessment for OraDisc™A, Amlexanox 2 mg, Mucoadhesive Patch as described in 21 CFR 25.31 (c). The firm provided the calculations to show EIC level well below 1 ppb. as per 21 CFR 25.31 (b).

B. Description of How the Drug Product is Intended to be Used

ROUTE OF ADMIN.: Topical

The OraDisc is placed on the mucosal tissue of mouth. The mucoadhesive polymers [ ] ensure the adhesion to mucosal tissue. The mucoadhesive layer swells upon contact with the saliva. While the backing layer is progressively dissolving and eroding into the saliva, the drug is being delivered at

the site of application. After subsequent erosion, the remaining pieces of the patch are dislodged and swallowed.

C. Basis for Approvability or Not-Approval Recommendation

The manufacturing and controls as identified above are sufficient to assure the consistent identity, strength, quality and purity of the drug product. However, there are some minor CMC and labeling issues that need resolution by the applicant.

III. Administrative

A. Reviewer's Signature:

B. Endorsement Block

Chemist Name/Date: Ernest G. Pappas/9/24/04
ChemistryTeamLeaderName/Date: Norman R. Schmuff /
ProjectManagerName/Date/ Jacquelyn Smith/

C. CC Block:

HFD-540/Division File
HFD-540/Pappas
HFD-540/Hyman
HFD-540/Lee
HFD-540/See
HFD-540/Chaurasia

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_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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/s/

Ernest G. Pappas
9/24/04 10:20:29 AM
CHEMIST

My chemistry review has been completed. This review contains the corrections to the IR Deficiencies observed. Recommend approval of the NDA from a CMC standpoint.

Norman Schmuff
9/24/04 11:16:03 AM
CHEMIST

1.3.6 Environment Assessment Waiver

Access Pharmaceuticals, Inc., hereby claims a categorical exclusion from the preparation of an Environmental Assessment for OraDisc™A, Amlexanox 2mg, Mucoadhesive Patch as described in 21 CFR 25.31(c).

David P. Nowotnik, Ph.D.
Senior Vice-President, Research & Development

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-727

Pharmacology Review(s)

PHARMACOLOGY/TOXICOLOGY COVER SHEET

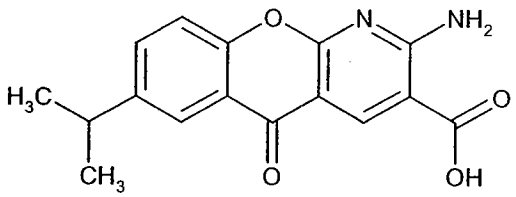
NDA number: 21-727
Review number: 1
Sequence number/date/type of submission: N-000/04-DEC-2003

Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Access Pharmaceuticals, Inc.
2600 Stemmons Freeway, Suite 176
Dallas, TX 75207
Manufacturer for drug substance:

Reviewer name: Norman A. See, Ph.D.
Division name: Division of Dermatologic and Dental Drug Products
HFD #: 540
Review completion date: 14-JUN-2004

Drug:

Trade name: Amlexanox 2 mg Mucoadhesive Patch
Generic names (list alphabetically): Amlexanox
Code name: AA-673; CHX 3673
Chemical names: 2-amino-7-isopropyl-5-oxo-5H-[1] benzopyrano [2,3-b] pyridine-3-carboxylic acid
CAS registry number:
Mole file numbers: NA
Molecular formula/molecular weights/structures: $C_{16}H_{14}N_2O_4$/298.3

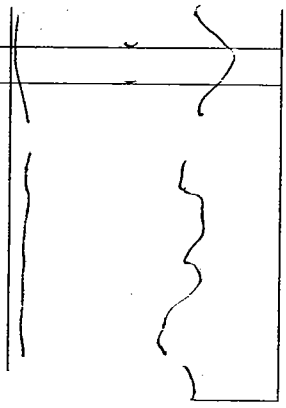


Relevant INDs/NDAs/DMFs: IND [redacted] IND [redacted] IND [redacted] IND 59,524; IND 59,949; IND [redacted] NDA 20-511

Drug class: Anti-inflammatory agent
Indication: Treatment of aphthous ulcers

Clinical formulation (per dosage unit):

Component	Amount
Amlexanox	2.00 mg
Ethylcellulose	[redacted]
Hypromellose (Hydroxypropyl methylcellulose)	[redacted]

Hypromellose film	
Povidone	
Hydroxyethylcellulose Carboxymethylcellulose sodium Polycarbophil Propylene glycol Sodium benzoate Purified water Red food color	

Route of administration: Topical to oral mucosa (and eventually swallowed)

Proposed use: The proposed use of the product involves placement of dosage units directly upon aphthous ulcers in the oral mucosa. One dosage unit is applied to each aphthous ulcer four times daily. The Dental Teamleader has estimated that a maximum of 20 units might be used per day in an individual with multiple ulcers (as a worst-case exposure estimate). A course of therapy would be expected to last approximately 7 days. Therefore, a course of therapy with the product would be expected to entail exposure to up to 40 mg amlexanox per day (0.67 mg/kg/day in a 60 kg patient) for 7 days. Development of aphthous ulcers is a recurring condition, and it is likely that a given individual would undergo numerous courses of therapy in a lifetime, resulting in chronic exposure to the product.

Introduction and drug history: Amlexanox oral paste 5% (Aphthasol) was approved under NDA 20-511 for treatment of aphthous ulcers on 17-DEC-1996. The label for Aphthasol provides for application of approximately 60 mg of paste to each aphthous ulcer four times daily for approximately 10 days. This equates to approximately 12 mg amlexanox per ulcer per day, applied to the oral tissues.

Amlexanox 50 mg tablets are approved in Japan (but not the U.S.) for treatment of asthma; a dosage of approximately 150 mg per day is typical.

Studies reviewed within this submission: The submission contained no new nonclinical data. The application references NDA 20-511. NDA 20-511 contains the following nonclinical studies (please see the attached review of NDA 20-511 for detailed review of the data; only the more relevant studies are listed):

1. Acute toxicology:

1.1. Acute toxicity of AA-673 in mice and rats, study report No. A-16-145, study No. 110/AC.

1.2 Acute oral toxicity study with rats, study report No. 70903807.

1.3 Acute dermal toxicity study in rabbits, study report No. 70903808.

2. Repeat dose toxicology.

2.1 Five-week oral toxicity study of AA-673 in rats, study report No. A-16-146, study No. 99/SU.

2.2 Twenty-six-week oral toxicity study of AA-673 in rats, study report No. A-16-185, study No. 143/CH.

2.3 Five-week oral toxicity study of AA-673 in beagle dogs, study report No. A-16-136, study No. 115/SU.

2.4 Five-week oral toxicity study of AA-673 in beagle dogs followed by 5- and 10-week recovery periods, study report No. A-16-485, study No. 304/SU.

2.5 Twenty-six-week oral toxicity study of AA-673 in beagle dogs, study report No. A-16-187, study No. 144/CH.

3. Genetic toxicology

3.1 Mutagenicity tests on amlexanox sodium salt (1): Rec-assay and reversion test in bacteria, study report No. A-16-541.

3.2 Micronucleus test on amlexanox (AA-673) in mice, study report No. A-16-476.

3.3 Mouse lymphoma mutation assay, study report No. 762164.

4. Carcinogenicity

4.1 18 month dietary oncogenicity study in mice with AA-673, study report No. A-16-498, study No. 295-060.

4.2 Two year dietary oncogenicity study in rats with AA-673, study report No. A-16-506, study No. 295-058.

5. Reproductive toxicology.

5.1 Effect of amlexanox (AA-673) on fertility and general reproductive performance of the rat, study report A-16-473.

5.2 Teratological study of amlexanox (AA-673) in the rat, study report No. A-16-472.

5.3 Teratological study of amlexanox (AA-673) in the rabbit, study report No. A-16-471.

5.4 Effect of amlexanox (AA-673) on peri- and post-natal development of the rat, study report No. A-16-474.

6. Special toxicology.

6.1 Nasal cavity irritation study of AA-673 nasal solution after forced deterioration in rats, study report No. A-16-527.

6.2 Nasal mucosal irritation study of AA-673 nasal solution after forced deterioration in rats, study report No. A-16-585.

6.3 Five-week toxicity study of AA-673 delivered into the nasal cavity in rats, study report A-16-274.

6.4 Ocular irritation study of AA-673 ophthalmic solution in frequent instillation in rabbits, study report No. AA-673/S-TX02.

6.5 The external ocular toxicity study of aged 0.25% AA-673 ophthalmic solution by 4-week repeated instillation in rabbits, study report No. AA-673/S-TX03.

6.6 Four-week ocular toxicity study of 0.5% AA-673 ophthalmic solution in rabbits, study report No. AA-673/S-TX01.

Studies not reviewed within this submission: The submission contained a number of photocopies of journal articles that were not specifically summarized in this review because they were judged to add no useful information to the database that was captured in the review.

Disclaimer: Tabular and graphical information is from sponsor's submission unless stated otherwise.

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Executive Summary

I. Recommendations

A. Recommendation on Approvability: This NDA is approvable with respect to pharmacologic and toxicologic concerns.

B. Recommendation for Nonclinical Studies: No additional nonclinical studies are recommended at this time.

C. Recommendations on Labeling: The following changes in the draft labeling are recommended:

1. Carcinogenesis, Mutagenesis, Impairment of Fertility: The text in this section should be stricken and replaced with:

"Amlexanox was not carcinogenic when administered to mice for 18 months at dosages up to 100 mg/kg/day (approximately 12 times the maximum human dose when comparing on the basis of body surface area estimates) or to rats for 24 months at dosages up to 250 mg/kg/day (approximately 60 times the maximum human dose). Amlexanox was negative in bacterial mutation assays in Salmonella, E. coli, and B. subtilis, in a mouse lymphoma assay, and in a micronucleus assay conducted in mice.

Amlexanox did not affect reproductive performance (fertility) or ability of rats to deliver and rear pups (perinatal development) when administered at dosages up to 300 mg/kg/day (approximately 70 times the maximum human dose).

2. Pregnancy. The text in this section should be stricken and replaced with:

"Pregnancy category B. Reproduction studies have been performed in rats and rabbits at doses up to 300 mg/kg/day (approximately 70 and 145 times the maximum human dose in rats and rabbits, respectively, when comparing on the basis of body surface area estimates) and have revealed no evidence of impaired fertility or harm to the fetus due to amlexanox. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed."

II. Summary of Nonclinical Findings

A. Brief Overview of Nonclinical Findings: Little potential for toxicity was observed in a battery of toxicology studies conducted with amlexanox that included acute, subchronic, chronic, carcinogenicity, genetic, and reproductive studies. No-effect-levels (NOELs) in these studies were substantial multiples of the proposed human exposure (please see the "Detailed Conclusions and Recommendations" section of this review, and the attached Pharmacology review of NDA 20-511, for additional information). No toxicity that appeared relevant to the proposed clinical use was observed.

B. Pharmacologic Activity: Amlexanox acts through an unknown mechanism that may involve inhibition of various mediators of inflammation and/or protease enzymes.

C. Nonclinical Safety Issues Relevant to Clinical Use: None

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PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY:

Please see the attached Pharmacology review No. 1 of NDA 20-511 for details of the pharmacology studies that support NDA 21-727.

Primary pharmacodynamics: The mechanism by which amlexanox acts is unknown. Amlexanox inhibits tissue necrosis factor-alpha, and this may be involved in increasing the rate of healing of aphthous ulcers. In vitro data suggest amlexanox may inhibit release of various mediators and enzymes, including IL-1β, IL-5, and inhibition of protease enzymes.

Mechanism of action: Unknown, although it has been suggested that amlexanox has anti-inflammatory properties.

Drug activity related to proposed indication: Unknown.

Secondary pharmacodynamics: NA

Pharmacology summary: Amlexanox acts through an unknown mechanism that may involve inhibition of various mediators of inflammation and/or protease enzymes.

Pharmacology conclusions: The mechanism of action of amlexanox is unknown.

II. SAFETY PHARMACOLOGY:

Please see the attached Pharmacology review No. 1 of NDA 20-511 for details of the safety pharmacology studies that support NDA 21-727.

III. PHARMACOKINETICS/TOXICOKINETICS:

Please see the attached Pharmacology review No. 1 of NDA 20-511 for details of the pharmacokinetics studies that support NDA 21-727.

IV. GENERAL TOXICOLOGY:

Please see the attached Pharmacology review No. 1 of NDA 20-511 for details of the toxicology studies that support NDA 21-727.

V. GENETIC TOXICOLOGY:

Please see the attached Pharmacology review No. 1 of NDA 20-511 for details of the studies, "mutagenicity tests on amlexanox sodium salt (1): Rec-assay and reversion test in bacteria" (study report No. A-16-541) and "micronucleus test on amlexanox (AA-673) in mice" (study report No. A-16-476). In addition, the sponsor has performed the following genetic toxicology study since NDA 20-511 was approved (the report of this study was submitted to IND 59,949):

Study Title: Mouse lymphoma mutation assay
Study No: 762164
Study Type: In vitro point mutation assay
Amendment #, Volume # and Page #: 001, 1, 078 (of IND 59,949)
Conducting Laboratory: [ ]
Date of Study Initiation/completion: In-life 28-APR-1998-11-JUN-1998; report dated 18-AUG-1998
GLP Compliance: Yes
QA- Reports Yes (X) No ( ):
Drug Lot Number: 1006-7113
Study Endpoint: Growth in medium containing trifluorothymidine (TFT), indicating mutation from tk^+tk^- to tk^-tk^-

Methodology:

- Strains/Species/Cell line: tk^+tk^- 3.7.2.C mouse lymphoma L5178Y cells
- Dose Selection Criteria: Cytotoxicity
  - Basis of dose selection: Cytotoxicity in range-finding studies
  - Range finding studies: Examined concentrations of amlexanox in culture medium ranging from 0.1 to 1000µg/mL, with and without S9
- Test Agent Stability: Chemical analysis of the test material formulations used in this study were not performed. However, data from previous studies with amlexanox suggest it was adequately stabile throughout the experimental period
- Metabolic Activation System: Aroclor 1254-induced S9 (supernatant of the post-mitochondrial 9000 g fraction from adult male Fischer rats)
- Controls:
  - Vehicle: DMSO in culture medium
  - Negative Controls: Vehicle
  - Positive Controls: Ethyl methanesulphonate and methyl methanesulphonate in absence of S9; 3-methylcholanthrene in presence of S9
  - Comments: Controls were adequate
- Exposure Conditions:
  - Incubation times: 4 hour exposure with and without S9; negative results in absence of S9 were repeated in a 24 hour exposure

- Doses used in definitive study: 10μg/mL-240μg/mL
- Study design: Following the exposure period, the cells were washed and grown for 9 to 12 days with and without TFT

- Analysis:
  - No. slides/plates/replicates/animals analyzed: 192 wells per concentration per assay
  - Counting method: Dissecting microscope
  - Cytotoxic endpoints: Reduced cell count in absence of TFT
  - Genetic toxicity endpoints: Increased numbers of cells that grew in presence of TFT

Results:

- Study Validity: Acceptable
- Study Outcome: Amlexanox did not increase the incidence of cell survival (colony formation) in medium that contained TFT in either the presence or absence of S9. Appropriate results were obtained with the controls.

Summary of individual study findings: Amlexanox was negative in a mouse lymphoma assay.

Genetic toxicology summary: Amlexanox was negative in a rec assay, an Ames assay, a mouse lymphoma assay, and a micronucleus assay.

Genetic toxicology conclusions: These data suggest that amlexanox is not genotoxic.

Labeling recommendations: See labeling portion of recommendations and conclusion, below.

VI. CARCINOGENICITY:

Please see the attached Pharmacology review No. 1 of NDA 20-511 for details of the toxicology studies that support NDA 21-727.

Carcinogenicity summary: Amlexanox was negative in carcinogenicity studies conducted in both mice and rats.

Carcinogenicity conclusions: These data suggest that amlexanox is not carcinogenic.

Labeling Recommendations: See labeling portion of recommendations and conclusion, below.

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:

Please see the attached Pharmacology review No. 1 of NDA 20-511 for details of the toxicology studies that support NDA 21-727.

Reproductive and developmental toxicology summary: Amlexanox was evaluated for potential to induce reproductive toxicity in a series of studies that included a fertility study in rats, teratology studies in rats and rabbits, and a perinatal development study in rats. No evidence of toxicity was observed.

Reproductive and developmental toxicology conclusions: These data suggest that amlexanox is not a reproductive toxicant.

Labeling recommendations: See labeling portion of recommendations and conclusion, below.

VIII. SPECIAL TOXICOLOGY STUDIES:

Please see the attached Pharmacology review No. 1 of NDA 20-511 for details of the toxicology studies that support NDA 21-727.

Special toxicology summary: Amlexanox was evaluated for potential to induce local irritation in studies that involved instillation of drug solutions into the nasal cavity and eye in rats and rabbits. The materials were judged to be essentially non-irritating.

Special toxicology conclusions: Drug solutions that contained amlexanox were judged to be essentially non-irritating.

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Conclusions: Amlexanox was evaluated in a series of toxicology studies that included acute, subchronic, chronic, carcinogenicity, genetic, and reproductive toxicology studies. Please see the attached Pharmacology review No. 1 of NDA 20-511 for details of the toxicology studies that support NDA 21-727. Briefly summarizing the pivotal studies:

Study Type	Study Summary
26 Week Rat	NOEL was 100 mg/kg/day (24 times the maximum clinical dose*); very little toxicity at 300 mg/kg/day (the highest dose used)
26 Week Dog	NOEL was 30 mg/kg/day (the highest dose used; 24 times the maximum clinical dose)
18 Month Mouse (Carcinogenicity)	NOEL was 30 mg/kg/day (4 times the maximum clinical dose); 100 mg/kg/day (the highest dose used) induced slight toxicity (small reduction in BW of males, reduced RBC parameters, and nephrosis, but no effect on survival)
24 Month Rat (Carcinogenicity	NOEL was 80 mg/kg/day (19 times the maximum clinical dose); 250 mg/kg/day (the highest dose used) induced minor liver toxicity, but no effect

)	on survival
Fertility, Rat (males dosed for 9 weeks prior to mating, females dosed starting two weeks prior to mating and then for remainder of study)	NOEL was 300 mg/kg/day (the highest dose used; approximately 70 times the maximum clinical dose)
Teratology, Rat	NOEL was 300 mg/kg/day (the highest dose used; approximately 70 times the maximum clinical dose)
Teratology, Rabbit	NOEL was 300 mg/kg/day (the highest dose used; approximately 145 times the maximum clinical dose)
Perinatal Development, Rat	NOEL was 300 mg/kg/day (the highest dose used; approximately 70 times the maximum clinical dose)

*Dose multiples are based upon body surface area estimates.

In addition, negative results were obtained when amlexanox was tested for genetic toxicity and carcinogenicity. Note that the NOEL (no effect level) values and dose-multiples offer a very conservative estimate of the safety margin, because: 1) they are from long-term studies, while a course of therapy with the product would be expected to entail exposure for only 7 days; and 2) the dose-multiples are based upon a worst-case scenario exposure to the drug product of 40 mg amlexanox per day (0.67 mg/kg/day in a 60 kg patient). The actual exposure of a given patient would probably be substantially less than this. Given the small magnitudes of the level and duration of the proposed exposure to amlexanox, and the relative lack of toxicity observed in nonclinical studies conducted with amlexanox (even at much higher exposure levels), the proposed exposure to amlexanox should be acceptably safe. Additional evidence of safety comes from the marketing history of amlexanox oral paste (NDA 20-511), which involves an essentially identical exposure to amlexanox. No serious adverse events have been reported during the approximately seven year marketing history of that product. All excipients in the proposed new product have been used in previously approved oral products, and are safe for the proposed new use.

Unresolved toxicology Issues (if any): NA

Recommendations: This NDA is approvable with respect to pharmacologic and toxicologic concerns. It is recommended that the labeling be revised as indicated below.

Labeling recommendations: The following changes in the draft labeling are recommended:

1. Carcinogenesis, Mutagenesis, Impairment of Fertility: The text in this section should be stricken and replaced with:

"Amlexanox was not carcinogenic when administered to mice for 18 months at dosages up to 100 mg/kg/day (approximately 12 times the maximum human dose when comparing on the basis of body surface area estimates) or to rats for 24 months at dosages up to 250 mg/kg/day (approximately 60 times the maximum human dose). Amlexanox was negative in bacterial mutation assays in Salmonella, E. coli, and B. subtilis, in a mouse lymphoma assay, and in a micronucleus assay conducted in mice.

Amlexanox did not affect reproductive performance (fertility) or ability of rats to deliver and rear pups (perinatal development) when administered at dosages up to 300 mg/kg/day (approximately 70 times the maximum human dose).

2. Pregnancy. The text in this section should be stricken and replaced with:

"Pregnancy category B. Reproduction studies have been performed in rats and rabbits at doses up to 300 mg/kg/day (approximately 70 and 145 times the maximum human dose in rats and rabbits, respectively, when comparing on the basis of body surface area estimates) and have revealed no evidence of impaired fertility or harm to the fetus due to amlexanox. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed."

Signatures (optional):

Reviewer Signature _____

Supervisor Signature _____ Concurrence Yes ___ No ___

X. APPENDIX/ATTACHMENTS:

Addendum to review: NA

Other relevant materials (Studies not reviewed, appended consults, etc.): Pharmacology review 1 of NDA 20-511 is attached, beginning on the next page.

Any compliance issues: NA

cc: list:
NDA 21-727
HFD-540
HFD-540/DivDirector/Wilkin
HFD-540/Deputy DivDirector/Kukich
HFD-540/SupPharm/Brown
HFD-540/Pharm/See
HFD-540/DO/Hyman
HFD-540/CMC/Pappas
HFD-540/PMS/Smith

Note: The following review of NDA 20-511 was written by John Wedig, Ph.D.

Evaluation of Pharmacology and Toxicology Data
Division of Topical Drug Products, HFD-540

NDA: # 20-511 (Resubmission Dated April 19, 1995)

Date Submitted: April 17, 1995

Date CDER Received: April 19, 1995

Assigned Date: April 21, 1995

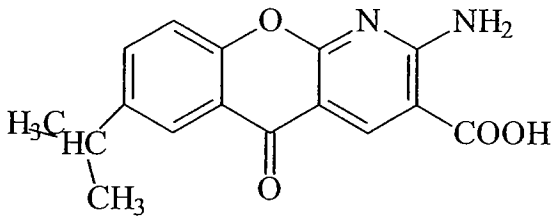
Date Review Completed:

Date Review Accepted By Supervisor:

Name of Drug: Amlexanox Oral Paste, 5% **Code Name:** AA-673; CHX 3673

Chemical Name: 2-amino-7-isopropyl-5-oxo-5H-[1] benzopyrano [2,3-b] pyridine-3-carboxylic acid

Structure:



Molecular Formula: $C_{16}H_{14}N_2O_4$

Molecular Weight: 298.30

Pharmacological Category: Antiallergic and anti-inflammatory; the mechanism of action for accelerating the healing of aphthous ulcers is unknown

Sponsor: Chemex Pharmaceuticals, Inc
Fort Lee Executive Park 1

Martha R. Charney, Ph.D.
Vice President, Regulatory Affairs

One Executive Drive
Ft. Lee, NJ 07024
Phone (201) 944-1449

Proposed Indication: Treatment of aphthous ulcers on the oral mucosal lining

Formulation:	Ingredient	Composition (% w/w)
	Amlexanox	5.0
	Mineral oil, USP	
Gelatin, NF		
	Pectin, NF	
	Carboxymethylcellulose sodium, USP	
	Carboxymethylcellulose sodium, USP	
	Glycerol monostearate, NF	
	White petrolatum, USP	
	Benzyl alcohol, NF	

Related Submissions: IND [redacted]
IND [redacted]
NDA 89-066 Stiefel Research
NDA 19-940 Actinex-Chemex
DMF [redacted]

Dosage Form and Route of Administration: The 5% oral paste (formulation noted above) is to be dabbed on the ulcer four times a day, preferably following oral hygiene after breakfast, lunch, dinner and at bedtime. The projected maximum human dose would be approximately 1mg/kg/day.

The pharmacology and pharmacokinetic studies have been previously summarized by Dr. Browder in the original review of IND 31,079 and amendment # 001. The following studies were reviewed under IND 34,787 by Dr. Morseth (see attached):

1) Acute Exposure Oral Toxicity Study With 5% CHX 3673 Cream (PH 402-CX-001-88; GLP).

2) Acute Exposure Dermal Toxicity Study In Rabbits With 5% CHX 3673 Cream (PH 22-CX-001-88; GLP).

3) Primary Dermal Irritation Study With 5% CHX 3673 Cream (PH 420-CX-001-88; GLP).

4) Delayed Contact Hypersensitivity Study In Guinea Pigs With CHX 3673 Cream (PH 424-CX-001-88; GLP).

5) Hamster Cheek Pouch Irritation Study (Multiple Dose) With CHX 3673 (PH 418-CX-001-90; GLP).

6) 8-Day Dermal Toxicity Study In Rabbits With CHX 3673 Cream (PH 430-CX-001-88)

Review Objectives: To assist in the safety evaluation of a 5% oral paste preparation for the treatment of aphthous ulcers by the evaluation of nonclinical laboratory studies for clinical studies.

Index Of Preclinical Studies:

Acute Evaluations
- Oral, dermal, skin and sensitization

Subacute Evaluations
- 5 Week Oral Toxicity Study In Rats
- 26 Week Oral Toxicity Study In Rats
- 5 Week Oral Toxicity Study In Beagle Dogs
- 5 Week Oral Toxicity Study In Beagle Dogs Followed By 5 And 10 Week Recovery Periods
- 26 Week Oral Toxicity Study In Beagle Dogs

Chronic Studies
- 18 Month Dietary Oncogenicity Study In Mice
- 2 Year Dietary Oncogenicity Study In Rats

Special Toxicity Studies
- Nasal Mucosal Irritation Study In Rats
- 5 Week Toxicity Study Of AA-673 Into The Nasal Cavity In Rats
- Ocular Irritation From Repeated Instillation
- Ocular Toxicity of Aged AA-673 Ophthalmic Solution-4 Weeks Of Instillation
- Four Week Ocular Toxicity of AA-673 Ophthalmic Solution In Rabbits

Reproductive Studies
- Segment I In Rats
- Segment II In Rats and Rabbits
- Segment III In The Rats

Mutagenicity Studies
- Ames Test
- Micronucleus Test-Mouse

Absorption And Kinetic Studies

Protein Binding And Erythrocyte Distribution

Tissue Distribution And Accumulation Studies

Enzyme Induction

Metabolism

Excretion

Nasal Administration

Intraocular Penetration

Acute Studies

1) Acute Toxicity Of AA-673 In Mice And Rats (Report # A-16-145, GLP)

Laboratory: [redacted]
Number of Animals: 10/sex/group
Animal Strain: Mice-Ta:ICR, Rats-Jcl:Wistar
The test material was suspended in 5% gum arabic. The animals were observed for 7 days after treatment and then necropsied. The LD50 (95% confidence limits) was found to be:

Mouse- mg/kg	Male	Female
Subcutaneous injection	3310(2960-3680)	3760(3370-4200)
Intraperitoneal injection	480(440-520)	450(410-490)
Oral gavage	2370(2160-2540)	2320(2120-2540)
RAT-mg/kg	Male	Female
Subcutaneous injection	1560(1320-1820)	1400(1180-1620)
Intraperitoneal injection	520(470-560)	500(460-540)
Oral gavage	ca 10000	ca 10000

A difference in LD50 values was noted between rats and mice. The major clinical signs noted after treatment were decreased activity and respiratory depression. The study is acceptable for its intended purpose.

2) Acute Oral Toxicity Study In Rats (Report # 70903807; GLP)

Laboratory: [redacted]

Number Of Animals: 5/sex/group

Animal Strain: Sprague Dawley, Charles Rivers

Study Design: The test material was suspended in 0.5% hydroxypropyl methylcellulose. The rats were observed for 14 days following dosing and then necropsied.

Results: The LD50(mg/kg) and 95% confidence limits were found to be : Male-5000(3346-7473) female-2828(1964-4073). Combined values were 3810 mg/kg. The major clinical sign noted after dosing was hypoactivity. The study is acceptable for its intended purpose.

3) Acute Dermal Toxicity Study In Rabbits (solution of Amlexanox; Report # 70903808 GLP)

Laboratory: [redacted]

Number Of Animals: 5 males and 5 females

Animal Strain: New Zealand Albino

Study Design: The test material was dissolved in trolamine and water to yield a 10% solution which was applied at 2 gm/kg. One-half of the animals had abraded skin sites. A pilot study using two animals per sex indicated no mortality.

Results: The study using 10 animals indicated no mortality at 2 gm/kg. This study is acceptable for its intended purpose.

4) Publication- Hairya, et al, Allergenicity and tolerogenicity of amlexanox in the guinea pig, Contact Dermatitis, 1994; 31: 31-36. Oral administration of amlexanox prior to sensitization resulted in complete non-responsiveness. It is proposed that a substantial reduction in the risk of sensitization from the use of an ophthalmic solution containing amlexanox may be achieved by the prior oral administration of tablets containing this drug.

Subacute Evaluations

1) Five Week Oral Toxicity Study of AA-673 In Rats (Report A-16-146; GLP)

Laboratory: [ ]

Number Of Animals: 10 males and 10 females per group

Animal Strain: Ta:Wistar [ ]

Dose Levels: 0, 40, 200 and 1000 mg/kg/day

Formulation: The compound was mixed with gum arabic and suspended in distilled water at concentrations of 0, 0.8, 4 and 10% (w/v) to correspond to the 0, 40, 200 and 1000 mg/kg doses-i.e. 10, 5, 5 and 10 ml/kg/ day respectively.

Route: Oral gavage once a day.

Study Design: The rats were dosed 7 days a week for 5 weeks. The water intake and 24 hour urine volume were determined for 5/sex/group at the beginning and end of the study. Body weight and food consumption was determined weekly. A urinalysis was performed on 5/sex/group toward the end of the treatment period. Hematology and serum chemistry was evaluated on all animals (fasted) at the termination of treatment. A piece of liver was taken at necropsy from 5/sex/group for determination of enzymatic activity. At necropsy 16 organs/animal were weighed from 10/sex/group and 21 tissues/animal were processed for histology from 5/sex/group. Kidney and liver tissue from one male in the control group and two males in the 1000 mg/kg group was examined with an electron microscope.

RESULTS

Mortality: One male in the 200 mg/kg group died during the course of the evaluation due to a technical dosing error-i.e. not treatment related .

Clinical Observations, Body weight, Food Consumption, Urinalysis, Urine Chemistry, Water Intake, Urine Volume, Hematology, Hepatic Drug Metabolizing Activity: No treatment related findings.

Organ And Organ-to-Body Weights: A significant increase in the mean absolute and relative to body organ weight was noted for the cecum and stomach in the animals treated with 1000 mg/kg. This was considered to be treatment related.

Serum Chemistry: The alkaline phosphatase levels were significantly increased in the males and females given 1000 mg/kg as compared to the controls. This was a treatment related effect not noted in other groups.

Gross Necropsy: A treatment related white-yellowish mucous was observed on the surface of the gastric mucosa of almost all females and one male in the 1000 mg/kg group. This was not noted in the other groups.

Histopathology: Treatment related findings included the following in the 1000 mg/kg group:

Glandular stomach-

6 animals- thickening of mucosa with hypersecretion
5 animals- dilation of glandular lumen

Forestomach-

2 animals- hyperplasia of mucosa

Cecum-

4 animals- hypertrophy and desquamation of epithelium

Electron Microscopy: A slight dilation of the bile cuniculi in the liver was seen at a dose of 1000 mg/kg.

Summary: The no adverse affect level of AA-673 from this evaluation is 200 mg/kg. The target organs appear to be the cecum and the glandular stomach at a dose of 1000 mg/kg-i.e. pathological changes and weight increases. Electron microscopic changes were noted in the liver and a significant elevation in serum alkaline phosphatase was noted at this dose level. All of these changes were minimal in nature. The study is acceptable for its intended purpose.

2) 26 Week Oral Toxicity Study Of AA-673 In Rats (Report # A-16-185; GLP)

Laboratory: [ ]

Number Of Animals: 12 males and 12 females per group

Animal Strain: Jcl:Wistar Rats

Dose Levels: 0, 30, 100 and 300 mg/kg/day

Formulation: Dietary admix. Test diets were made up weekly.

Route: Oral

Study Design: Animals were fed diets containing the drug for 26 weeks. Clinical signs were monitored daily, food consumption 2 X week and body weight weekly. Five males and 5 females had a urinalysis done pretest and during weeks 6, 14 and 26. Hematology and serum chemistry evaluations were done on fasted animals at necropsy. All animals were necropsied and organ weights were obtained. Histopathological evaluation was done on 5 males and 5 females from each group. Liver from the control and the 100 and 300 mg/kg groups was examined under an electron microscope.

RESULTS

Mortality: No treatment related mortality occurred. There were two incidental deaths.

Diet Analysis: Concentrations of AA-673 were analyzed during weeks 5, 10, 15, 20 and 25 and found to be within 88 to 113% of theoretical. AA-673 was stable in the [ ] rat chow for 2 weeks at room temperature. No homogeneity data were given.

Dietary Intake: The group mean dietary intakes were close to theoretical. Some of the ranges were outside of 10%.

Clinical Observations, Urinalysis, Hematology, Body Weight, Gross Necropsy Observations and Histopathological Analysis:
No treatment related effects were noted on any of these parameters.

Food Consumption: Males in the 300 mg/kg group consumed significantly more food than the control animals for most weekly periods up through 15 weeks. Females receiving the same dose did not.

Organ Weights: An increase in the cecum weight was noted only in the males receiving 100 and 300 mg/kg. No histopathological change was seen in the cecum or the other parts of the gastrointestinal tract indicating this effect was not treatment related.

Serum Chemistry: A significant increase was noted in the mean alkaline phosphatase levels only in the males given 300 mg/kg.

Electron Microscopy: A slight dilatation of the bile canaliculi in the centrolobular hepatocytes was seen in one male given 300 mg/kg and was considered to be treatment related.

Summary: The no effect level of AA-673 appears to be 100 mg/kg due to the elevated serum alkaline phosphatase and the dilated bile cuniculi in the males given 300 mg/kg. The study is acceptable for its intended purpose.

3) Five Week Oral Toxicity Study Of AA-673 In Beagle Dogs (Report A-16-136; GLP)

Laboratory: [ ]

Number Of Animals: 3 males and 3 females per group

Animal Strain: Canine, beagle; [ ]

Dose Levels: 0, 10, 30 and 100 mg/kg/day

Route: Orally in the morning by gelatin capsule containing the pure drug

Study Design: The dogs were dosed 7 days a week for 5 weeks. Food consumption was determined daily and body weight 2 x weekly. Clinical observations were done pre dose and 1 and 6 hours post dosing. Physicals, ophthalmic examinations (internal and external), hematology evaluations including clotting times, urinalysis and water intake were done pretest, during the midpoint and at the end of the study. Serum chemistry was done pretest and weekly. Blood for plasma drug levels was taken 2, 10 and 24 hours post dosing on drug day 36. Liver tissue from all dogs was assayed for drug metabolism (hydroxylase and N-demethylase). Organ weights were obtained at necropsy from all animals and 25 tissues/animal were prepared for histological examination. Selected liver samples were silver stained and selected liver and kidney tissues were prepared for enzyme histochemistry.

RESULTS

Mortality: No treatment related deaths occurred.

Body Weight, Clinical Signs, Food Consumption, Physical Examinations, Ophthalmological Examinations, Hematology and Prothrombin Times, Urinalysis, Water Intake, Hepatic Drug Metabolism, Organ Weights, Hepatic Silver Stains and Enzyme Histochemistry of Kidney:
No consistent or distinct treatment related effects were noted.

Serum Chemistry: Ornithine carbamyl transferase, alkaline phosphatase and glutamic pyruvic transaminase were increased in the 100 mg/kg group. This was treatment related.

Plasma Levels Of AA-673: Peak plasma concentrations were reached about 2 hours post dosing. The drug blood concentrations indicated that the increase in plasma levels was greater than the increase in dose.

Gross Necropsy: A slight discoloration of the liver in two males and two females given 100 mg/kg was noted.

Histopathology: Treatment related finding in the 100 mg/kg group included- Proliferation of the bile ducts accompanied by fibroplasia in the peripheral zone of the liver lobule; atrophy and degeneration of the hepatocytes in close proximity to this lesion; hypertrophy of the epithelium of the gallbladder.

Enzyme Histochemistry: An increase in alkaline phosphatase activity of the proliferated bile ducts was noted in animals given 100 mg/kg.

Summary: Hepatotoxicity was noted at the 100 mg/kg dose. The no effect level appears to be 30 mg/kg. This study is acceptable for its intended purpose.

4) Five Week Oral Toxicity Study Of AA-673 In Beagle Dogs Followed By 5 And 10 Week Recovery Periods (Report # A-16-486; GLP)

Laboratory: [redacted]

Number Of Animals: 6 females in the control group and 9 females in the treatment group

Animal Strain: Canine, beagle [redacted]

Dose Level: 0 and 100 mg/kg

Route: Orally in the morning by gelatin capsule containing the pure drug

Study Design: The dogs were dosed 7 days a week for 5 weeks followed by a recovery period of 5 and 10 weeks. Food consumption and clinical observations were done daily. Serum chemistry was done pretest and at the end of the dosing and recovery periods. Two control and three treated animals were necropsied at the end of treatment and after 5 and 10 weeks of no dosing. Organ weights were obtained at the end of the AA-673 dosing period and the 5 week recovery period. Liver and gallbladder tissue were prepared for histological examination. Liver tissue was prepared for enzyme histochemistry and electron microscopic examination.

RESULTS

Mortality: No treatment related mortality occurred.

Clinical Signs: Most of the AA-673 dosed animals occasionally vomited undigested food throughout the treatment period.

Body Weight: Some animals showed a slight decrease during the dosing period which returned to expected values during the recovery period.

Serum Chemistry: Ornithine carbamyl transferase, alkaline phosphatase and glutamic pyruvic transaminase were increased in the treated animals at the end of the dosing period. The values were in the expected range 5 weeks after cessation of dosing.

Gross Necropsy: A slight discoloration of the liver surface was noted in 2 of the treated dogs after 5 weeks of dosing. This was not noted in any of the recovery dogs.

Histopathology: Hypertrophy of the bile duct epithelium, proliferation of peri-bile duct connective tissue and atrophy of hepatocytes around interlobular connective tissue was noted in all of the treated animals. After 5 weeks of recovery the only finding was a slight increase in the interlobular connective tissue in one dog. This change was not observed after 10 weeks of recovery.

Enzyme Histochemistry: A marked increase of alkaline phosphatase activity was noted in the bile cuniculi of the 3 treated dogs. This activity returned to expected values after the 5 week recovery period.

Electron Microscopy: A protrusion of hepatocytes into the bile cuniculi noted at the end of the dosing period was absent in the dogs after 5 weeks of recovery.

Summary: Hepatotoxicity noted after treatment with 100 mg/kg for 5 weeks was absent 10 weeks after no dosing, indicating complete recovery. The study is acceptable for its intended purpose.

5) 26 Week Oral Toxicity Study In Beagle Dogs (Report # A-16-187; GLP)

Laboratory: [redacted]

Number Of Animals: 3/ sex/group

Animal Strain: Canine, beagle, [redacted]

Dose Level: 0, 3, 10 and 30 mg/kg/day

Route: Orally in the morning by gelatin capsule containing the pure drug

Study Design: The dogs were dosed 7 days a week for 26 weeks. Food consumption was determined daily and body weight approximately weekly. Clinical observations were done pre dose and 1 and 6 hours post dosing. Physicals, ophthalmic examinations (internal and external), hematology, prothrombin times, serum chemistry, urinalysis, 24-hour water intake and urine volume were done pretest and during weeks 5, 13 and 26. All animals were subjected to a complete necropsy and their organs were weighed. Tissues from all animals were examined histologically. Enzyme histochemistry was done on liver tissue from all treatment groups. Liver tissue from the control and 30 mg/kg group was examined with an electron microscope.

RESULTS

Mortality, Body Weight, Food Consumption, Clinical Signs, Physical Examinations, Ophthalmological Examinations, Hematology, Prothrombin Times, Serum Chemistry, Urinalysis, 24-Hour Water Intake and Urine Volume, Gross Necropsy, Organ Weight, Histopathology and Electron Microscopy:

No consistent or distinct treatment related changes were noted.

Enzyme Histochemistry: A slight increase in alkaline phosphatase in the bile cuniculi of the central part of the liver lobule of one of two males in the 30 mg/kg group was noted.

Summary: The maximum non-toxic dose level in this evaluation was 30 mg/kg. This study is acceptable for its intended purpose.

CHRONIC STUDIES

1) 18 Month Dietary Oncogenicity Study In Mice With AA-673 (Report # 295-060; GLP)

Laboratory: [redacted]

Number Of Animals: 50/sex/group; 6 weeks old at study initiation

Animal Strain: mouse, $B_6C_3F_1$, [redacted]

Dose Levels: 0, 3, 10, 30 and 100 mg/kg

Formulation: Dietary admix. Test diets were made up weekly. Homogeneity studies indicated a 20 minute mix resulted in preparations that assayed plus or minus 10% of theory for AA-673 consistently. Stability studies indicated the AA-673 was stable(plus or minus 5% of theory) in [redacted] Chow [redacted] under laboratory conditions over a period of

10 days. The two lots of AA-673 used for mixing the diets were assayed at the beginning of each use span and found to be 99.9% pure. The sponsor provided analytical data indicating that AA-673 was stable at room temperature for at least two years.

Pilot Study: A 17 week dietary dose range finding study in this strain of mouse was conducted at [ ] using dose levels of 0, 25, 50, 100, 200, 500 and 1500 mg/kg (the latter two dosage levels from study week 14, and representing a change in the 25 and 50 mg/kg/day dose levels). A treatment related toxic nephrosis was noted beginning at a dose of 100 mg/kg . This effect increased in incidence and severity with increasing dose. No other treatment related effects were seen.

Study Design: Animals were fed the diets for 78 weeks. Food consumption and bodyweight were determined pretest, weekly during the first 14 weeks and thereafter every 2 weeks. Food efficiency was determined for the first 14 weeks. Clinical observations were done daily. Hematology evaluations were done at term and if possible on animals in extremis. All animals were subjected to a complete necropsy. A complete set of tissues was prepared for histopathological evaluation from the control and 100 mg/kg dose group, all animals that died or were sacrificed in extremis, plus all tissue masses with regional lymph nodes, gross lesions and the kidneys from the 3, 10 and 30 mg/kg groups.

RESULTS

Compound Consumption and diet analysis: The mean weekly compound consumption of all the AA-673 treated groups was within 10% of theory except for four instances during the 78 week treatment period. Diet assays every four weeks for AA-673 concentration in all groups indicated only six diet mixes that were greater or less than 10% of theory.

Mortality, Clinical Signs and Food Consumption: No treatment related effects were noted on these parameters.

Body Weight: No consistent treatment related effect was noted. In the males given 100 mg/kg there was a decrease in body weight in the last 6 months of treatment.

Hematology: A significant decrease in erythrocytes, hemoglobin and hematocrit were noted in the males given 100 mg/kg. This was not noted in the corresponding female group.

Gross Necropsy Observations: Males in the 100 mg/kg group had an incidence of 35/50 with granular kidneys. This treatment related effect was not noted in the females.

Histology: Toxic nephrosis of the kidney was noted in 50/50 males in the 100 mg/kg group.

Summary: The test material, AA-673, was determined to have no tumorigenic effect. The no effect level for toxicity to the kidney was 30 mg/kg. This study is acceptable for its intended purpose.

2) Two Year Dietary Oncogenicity Study In Rats With AA-673 (Report # 295-058; GLP)

Laboratory: [ ]

Number Of Animals: 50/sex/group; 5 weeks old at study initiation

Animal Strain: [ ] Fisher 344 rats [ ]

Dose Levels: 0, 25, 80 and 250 mg/kg/day

Formulation: Dietary admix. Test diets were made up weekly. Homogeneity studies indicated a 10 minute mix resulted in preparations that assayed plus or minus 10% of theory for AA-673 consistently. Stability studies indicated the AA-673 was stable (plus or minus 5% of theory) in [ ] Chow [ ] under laboratory conditions over a period of 10 days. The three lots of AA-673 used for mixing the diets was assayed at the beginning of each treatment span and found to be 99.9% pure. The sponsor provided analytical data indicating that AA-673 was stable at room temperature for at least two years.

Pilot Study: A 13 week dietary ranging finding study in Fisher 344 rats was conducted at [ ] using dose levels of 0, 125, 250, 500 and 1000 mg/kg. Body weight was decreased at 1000 mg/kg. Serum levels of alkaline phosphatase, glutamic oxaloacetic transaminase and glutamic pyruvic transaminase were increased in the males given 500 mg/kg and in both sexes at 1000 mg/kg. Histopathological evaluation of the liver indicated dilation of the extrahepatic and common bile ducts, bile duct hyperplasia, cholangitis, necrosis and pericholangitis. These were seen in both sexes at 1000 mg/kg and in the males at 500 mg/kg. Females at 500 mg/kg indicated only one trace instance of pericholangitis as did the males at 250 mg/kg. The dose of 125 mg/kg did not appear to produce any toxic effects.

Study Design: Animals were fed the diets for 104 weeks. Food consumption and body weight were determined pretest, weekly during the first 14 weeks and thereafter every 2 weeks. Food efficiency was determined for the first 14 weeks. Clinical observations were done daily. The animals were palpated for masses weekly. Hematology evaluations were performed on animals at term and on ones that were sacrificed in extremis. All animals were subjected to a complete necropsy. A complete set of tissues was prepared for histological evaluation from the control and 250 mg/kg dose group and all animals that died during the course of the study or were sacrificed in extremis. All tissue masses with

regional lymph nodes, all gross lesions, liver and adrenals from all animals were also prepared for histopathological examination.

RESULTS

Compound Consumption And Diet Analysis: The mean compound consumption of all the AA-673 treated groups was within 10% of theory except for three 2 week periods when it exceeded the 10% over the 104 weeks period. Diet assays every four weeks for AA-673 concentration in all groups indicated 14 values which were less than 10% of theory-i.e. 11 in the 80's and 3 in the high 70's.

Mortality, Hematology, Clinical Signs , Food Consumption And Food Efficiency: No treatment related effects were noted on these parameters.

Body Weight: There was a frequent significant decrease in body weight of the males given 250 mg/kg the second half of the study. The actual difference was small, 6%. This was occasionally noted in the high dose females.

Gross Necropsy Observations: Dilatation of the extrahepatic bile duct was noted in males given 250 mg/kg as well as an increase in eye lens discoloration.

Histology: Prominent biliary changes were noted in the males from the 250 mg/kg group. They included cystic dilatation, calculus formation and inflammation of the extrahepatic bile duct. Cholangitis and pericholangitis was noted in the liver. This effect was limited to a slight increase in pericholangitis in the females given 250 mg/kg.

Summary: The test material AA-673 was determined not to be carcinogenic. The no effect level for toxicity was determined to be 80 mg/kg. This study is acceptable for its intended purpose. See attached CAC forms for the rat and mouse.

SPECIAL TOXICITY STUDIES

1) Nasal Cavity Irritation Study Of AA-673 Nasal Solution After Forced Deterioration (Report # A-16-527). Only a summary report was available. The irritation potential of a deteriorated sample of AA-673 introduced into the nasal cavity of Jcl:Wistar rats 4 X/day for 14 days was evaluated. It was concluded that no irritation was produced by the deteriorated AA-673 applied to the nasal mucosa of rats under the test conditions.

2) Nasal Mucosal Irritation Study Of AA-673 Nasal Solution After Forced Deterioration In Rats (Report # A-16-585;GLP)

Laboratory: [ ]

Number Of Animals: 110/group

Animal Strain: Jcl:Sprague Dawley Rats
Duration Of Dosing: every 15 minutes for a total of nine times in one group
every 2 hours daily for 14 consecutive days

Dose Levels: 25 ul instilled in the left nostril per dose-AA-673 nasal solution or saline

Study Design: The animals were dosed and observed for clinical signs twice daily during the treastment period and once daily during the following observation period. They were weighed weekly. One and 7 days after the last instillation, 5 animals/group were sacrificed. The nasal area was prepared for histological examination.

RESULTS

No abnormalities were noted in clinical signs or at autopsy in either group of treated rats. Histopathological examination of the nasal tissues indicated that AA-673 did not cause irritation.

Summary: A deteriorated AA-673 nasal solution does not cause irritation to the nasal tissues. The study is acceptable for its intended purpose.

3) Five Week Toxicity Study Of AA-673 Delivered Into The Nasal Cavity In Rats (Report # A- 16-274; GLP)

Laboratory: [ ]

Number Of Animals: 5/sex/group

Animal Strain: Jcl:Sprague Dawley Rats [ ]

Duration Of Dosing: 5 Weeks, 7 days a week, 4 times a day. Each dose volume was 0.025 mL

Dose Levels: Saline control, 0.1 mL/rat/day
vehicle control, 0.1 mL/rat/day
AA-673 0.1 mg/rat/day; 0.1 mL/rat/day
AA-673 0.25 mg/rat/day; 0.1 mL/rat/day

Route: The solution was delivered 4 times a day to the left nasal cavity by means of a micropipette through the nostril.

Study Design: Animals were treated 4 times a day for 5 weeks. Clinical observations were noted daily. Body weights were taken on the 0, 1st, 3rd and 7th day and then twice weekly. A complete necropsy was conduced on each animal and the organs were weighed. The upper respiratory tract of each animal was prepared for histology and stained with three stains.

RESULTS

Mortality, Body Weight, Clinical Observations, Organ Weights and Gross Necropsy Observations:
No treatment related effects were note.

Histopathology: A very slight increase in the number of goblet cells in the respiratory region of the nose was noted in the animals treated with 0.25 mg/rat/day. However, there was no dose response relationship and this effect was also seen in the vehicle and saline controls. There were no changes indicative of degeneration of the cells.

Summary: The local irritative effect of AA-673 solution is very slight. The study is acceptable for its intended purpose.

4) Ocular Irritation Study Of AA-673 Ophthalmic Solution In Frequent Instillation In Rabbits (Report # AA-673/S-TX02)

Laboratory: [redacted]

Number Of Animals: 9

Animal Strain: Japanese white aboriginal rabbits

Dose : several drops of the 1.0% AA-673 ophthalmic solution

Route: instillation in the conjunctival sac of the right eye

Study Design:

Group 1- 3 rabbits- 32 topical installations in the eye at 15 minute intervals for a day

Group 2- 3 rabbits- 16 topical installations in the eye at 30 minute intervals for a day

Group 3- 3 rabbits- not used

The eyes were examined before treatment and 30 minutes after the last treatment. The cornea was stained with fluorescein dye and examined at these times. The animals behavior was also monitored.

RESULTS

Chemosis and redness of the conjunctivae and discharge were noted. No lesions were produced. The irritation cleared up 24 hours after the last instillation. The study is acceptable for its intended purpose

5) The External Ocular Toxicity Study Of Aged 0.25% AA-673 Ophthalmic Solution By 4 Week Repeated Instillation In Rabbits(Report # AA-673/S-TX03)

Laboratory: [ ]

Number Of Animals: 5 males

Animal Strain: Japanese white rabbits

Dose : Two drops of an aged (5 days) 0.25% AA-673 solution or physiological saline

Route: Instillation in the eye

Study Design: Animals had AA-673 (right eye) or saline (left eye) instilled onto the eye 9 times daily at 1 hour intervals for 28 days. The eyes were scored with the Draize procedure pretest and 30 minutes after the last instillation on days 1, 3, 7, 14, 21 and 28. Slit lamp examination with fluorescein staining followed the same schedule. Body weights were taken pretest and weekly and clinical observations were done daily.

RESULTS

The aged AA-673 0.25% solution had no effect on the rabbit eye or other parameters measured. This study is acceptable for its intended purpose.

6) Four Week Ocular Toxicity Study Of 0.5% AA-673 Ophthalmic Solution In Rabbits (Report # AA-673/S-TX01)

Laboratory: [ ]

Number Of Animals: 10

Animal Strain: Japanese white aboriginal rabbits

Dose Levels: 2 drops/dose (about 0.1 mL) ; 5 rabbits received AA-673 and 5 received saline

Formulation: 0.5% AA-673 ophthalmic solution or physiological saline

Route: conjunctival; AA-673 or physiological saline was put in the right eye; left eye was untreated

Study Design: The animals had either the drug or saline instilled onto the conjunctivae 9 times a day at 1 hour intervals for 29 days. The eye was scored using the Draize procedure and the cornea was examined using fluorescein and a slit lamp pretest and 1, 3, 7, 14, 21 and 28 days after study initiation. The pupil size and intraocular pressure was measured 2, 4 and 7 days prior to study termination Body weight and general condition were noted pretest and weekly thereafter.

RESULTS

No treatment related effects were noted on any of the parameters measures during the 29 day study. The study is acceptable for its intended purpose.

Reproductive Studies

1) Effect Of Amlexanox (AA-673) On Fertility And General Reproductive Performance Of The Rat (Report # A-16-473; GLP)

Laboratory: [ ]

Number Of Animals: 26 males and 26 females per group

Animal Strain: Jcl:Wistar [ ]

Dose Level: 0, 30, 100 and 300 mg/kg

Route: Oral intubation

Formulation: The drug was suspended in 5% gum arabic solution at a concentration of 6%. It was further diluted with 5% gum arabic to make 2 and 0.6% (w/v) suspensions. The controls received a 5% gum arabic solution. The dose volume to each group was 5 ml/kg. The doses were made up fresh daily. The dosing solutions were assayed pretreatment and 3 X during the study. All assays were well within plus or minus 10% of theory. Homogeneity and stability for 24 hours were determined and found to be within plus or minus 10% of theory.

Study Design: The males were treated daily for 9 weeks prior to mating. The females were treated daily for 2 weeks before mating and during the mating period. Dosing continued throughout the remainder of the study. Approximately one-half of the females were killed on day 13 of pregnancy, the remainder were allowed to rear their litters to day 22 after delivery. Food consumption, body weight, estrous cycle, copulation rate, conception rate, fertility index and various other reproductive indices were monitored.

RESULTS

Mortality, Body Weight, Food Consumption, Estrous Cycle, Conception Rate, Pre-Implantation Loss, Post- Implantation Loss, Number Of Corpora Lutea, Number Of Live Embryos, Morphological Observations, Development Of Maturational Landmarks, Gestation Period, Parturition, Suckling, Litter Size, Pup Mortality and Body Weight

No treatment related effects were noted on any of these parameters- reproductive performance or pre and post natal development of the pups. The study is acceptable for its intended purpose.

2) Teratological Study of Amlexanox (AA-673) In The Rat (Report # A-16-472; GLP)

Laboratory: [ ]

Number Of Animals: Approximately 49 pregnant females per group

Animal Strain: Jcl:Wistar Rat, [ ]

Dose Levels: 0, 30, 100 and 300 mg/kg

Route: Oral intubation

Formulation: The drug was suspended in 5% gum arabic solution at a concentration of 6%. It was further diluted with 5% gum arabic to make 2 and 0.6% (w/v) suspensions. The controls received a 5% gum arabic solution. The dose volume to each group was 5 ml/kg. The doses were made up fresh daily. The dosing solutions were assayed

pretreatment and 1 X during the study. Assays were well within plus or minus 10% of theory. Homogeneity and stability for 24 hours were determined and found to be within plus or minus 10% of theory.

Study Design: The animals were mated at [ ] The rats were treated on days 6-17 of pregnancy. Twenty-one to 23 per group were necropsied on day 20 of gestation. Two-thirds of the fetuses were stained for skeletal examination. The remaining one-third were examined for visceral abnormalities using the freehand sectioning technique of Wilson. Various reproductive indices, food consumption, body weight, behavior and mortality were calculated. The remaining 12 to 13 animals in each group were allowed to deliver. All dams were necropsied on day 22 or 23 postpartum- the number of implantation sites was counted and the main organs were examined histologically. The pups were sexed, weighed and their development assessed morphologically-pinna detatchment, incisor eruption and eye opening. Two males and two females from each litter in all dose groups were necropsied and examined for internal and skeletal (x-ray) abnormalities. One male and 1 female were examined microscopically for evidence of brain abnormalities. The remaining pups were reserved for behavioral and reproductive studies. The behavioral studies included- an open field test, water T-maze test and a wheel rotation activity test. The reproductive performance test involved - mating non-litter mates, allowing them to deliver. The pups were sacrificed on days 9 to 11. The main organs were examined histologically. An assessment of internal and skeletal development was made as well as a histological examination of the brain. The reproductive organs were examined thoroughly.

RESULTS

Mortality, Skeletal Development, Development Of The Internal Organs, Brain Development, Body Weight, Food Consumption, Litter Size, Pup Weight, Morphological Development, Number Of Implants, Number Of Resorptions, Maturational Landmarks and Behavior

No consistent or distinct treatment related effects were noted. The study is acceptable for its intended purpose.

3) Teratological Study Of Amlexanox (AA-673) In The Rabbit (Report # A-16-471; GLP)

Laboratory: [ ]

Number Of Animals: Approximately 12 to 14 pregnant females per group

Animal Strain: KBL:JW rabbit [ ]

Dose Levels: 0, 30, 100 and 300 mg/kg

Pilot Study: A two week oral intubation in females of this strain of rabbit was conducted. All of the animals given 1000 mg/kg died. Two of 5 animals in the 300 mg/kg group showed a decrease in food consumption. On this basis the above doses were selected.

Route: Oral intubation

Formulation: The drug was suspended in 5% gum arabic solution at a concentration of 3%. It was further diluted with 5% gum arabic to make 1 and 0.3% (w/v) suspensions. The controls received a 5% gum arabic solution. The dose volume to each group was 10 ml/kg. The doses were made up fresh daily. The dosing solutions were assayed pretreatment and 2 X during the study. Assays were well within plus or minus 10% of theory. Homogeneity and stability of 0.6 and 6.0% (w/v) suspensions for 24 hours were determined previously and found to be within plus or minus 10% of theory.

Study Design: The animals were mated at [ ] They were treated from day 6 through day 18 of pregnancy. Food consumption and body weights were obtained on days 0, 6, 13, 19, 23 and 28 of gestation. All animals were observed for signs of toxicity daily. The dams were necropsied on day 28 of gestation. Various reproductive indices were noted. The placenta, amnion and amniotic fluid were examined microscopically. The fetuses were examined for external and visceral abnormalities and variations. The heart and kidneys were freehand sectioned with a razor blade and examined for abnormalities. The fetuses were then stained for skeletal examination of potential abnormalities and variations. Prior to preparing the fetus for skeletal staining the head was freehand sectioned with a razor blade and the brain was examined for abnormalities.

RESULTS

Mortality, Skeletal Development, Development Of The Internal Organs, Brain Development, Body Weight, Food Consumption, Litter Size, Pup Weight, Number Of Implants, Number Of Resorptions And Histological Examination Of Organs

No consistent or distinct treatment related teratogenic or embryolethal effects were noted. A slight decrease in body weight gain and suppression of food consumption were noted in a few of the dams in the 300 mg/kg group the latter half of the treatment period. The study is acceptable for its intended purpose.

4) Effect Of Amlexanox (AA-673) On Peri- And Post-Natal Development Of The Rat (Report # A-16-474; GLP)

Laboratory: [ ]

Number Of Animals: 23 to 24 pregnant females per dose group

Animal Strain: Jcl:Wistar rat, [ ]

Dose Levels: 0, 30, 100 and 300 mg/kg/day

Pilot Studies: A 5 week oral toxicity study in rats indicated a no effect level of 200 mg/kg. An adverse effect was noted at 300 mg/kg in a 26 week oral rat study.

Route: Oral intubation

Formulation: The drug was suspended in 5% gum arabic solution at a concentration of 6%. It was further diluted with 5% gum arabic to make 2 and 0.6% (w/v) suspensions. The controls received a 5% gum arabic solution. The dose volume for each group was 5 ml/kg. The doses were made up fresh daily. The dosing solutions were assayed pretreatment and 2 x during the study. Assays were well within plus or minus 10% of theory. Homogeneity and stability of 0.6 and 6.0% (w/v) suspensions for 24 hours were determined previously and found to be within plus or minus 10% of theory.

Study Design: The pregnant rats were dosed from day 15 of pregnancy through suckling to day 21 postpartum. All animals were allowed to deliver and the F1 pups were examined for morphological development and assessed in behavioral tests- negative geotaxis and grip strength.. The dams were necropsied on day 22-23 postpartum and the number of implantation sites counted. Two males and two females were necropsied at the same time and examined for external and internal abnormalities, skeletal and brain abnormalities. The remaining F1 pups after weaning were assessed for testes descent and vaginal opening and then a select few from each litter were used for behavioral and reproductive performance studies. Behavioral studies included pupillary reflex, pain response, rotarod performance, open field test, preyer's reflex, running wheel activity test and the water T-maze test. All F2 pups were necropsied on days 7 to 9 postpartum . Selected animals were examined for skeletal abnormalities and variations and brain abnormalities. The presence or absence of sperm in the epidimides and follicles and luteinization in the ovaries was determined.

RESULTS

Mortality, Motor Coordination, Grip Strength, Numbers Of Newborn per Litter, Number Of Implantation Sites, Number Of Resorptions, Sex Ratio, Reflexes, Pain Response, Auditory Response, Rotarod Performance, Clinical Signs, Body Weight, Copulation Rate, Gestation Period, Delivery, Nursing, Conception Rate, Skeletal Or Visceral Abnormalities and Brain Abnormalities

Summary: No treatment related changes were noted on any of the above mentioned parameters. This study is acceptable for its intended purpose.

Mutagenicity Studies

1) Mutagenicity Tests On Amlexanox Sodium Salt (1): Rec-assay And Reversion Test In Bacteria (report # A-16-541)

Laboratory: [redacted]

Study Design: Two bacterial mutagenic assays were used to assess the drug- a repair test (modified rec assay) and a reverse mutation test (Ames test). Nine positive control agents were used and demonstrated to be active. The test strains for the repair test were B subtilis H17(rec+) and M45(rec-) and for the reverse mutation test were E. coli WP2uvrA and S. typhimurium TA100, TA98 and TA1537.

RESULTS

Negative results were obtained in the rec-assay at dosages of 125 and 1250 ug/disk. In the reverse mutation assay at dosages ranging from 100 to 5000 ug/plate negative results were obtained with and without metabolic activation (S9 fraction). It was concluded that the drug is not mutagenic or DNA damaging. The study is acceptable for its intended purpose.

2) Micronucleus Test On Amlexanox (AA-673) In Mice (Report # A-16-476; GLP)

Laboratory: [redacted]

Number Of Animals: 5 males/group

Animal Strain: SPF (C3HxSWV)F1, [redacted]

Dose Level: Single oral dose 0, 125, 500 and 2000 mg/kg
Single dose daily for four days 0 and 500 mg/kg

Formulation: Amlexanox was suspended in %5 gum arabic solution at 1.25, 5 and 20 %(w/v) such that all animals were given 10 mL/kg. Homogeneity and stability studies over 24 hours for this concentration range were acceptable-i.e. plus or minus 10% of theory.

Study Design: The drug was administered orally in a single dose at 0, 125, 500 and 2000 mg/kg or 0 and 500 mg/kg daily doses for 4 consecutive days. Mitomycin C, the positive control, was injected once intrapertioneally at a dose of 2 mg/5 mL/ kg. The animals were killed 30 hours after treatment and bone marrow was removed from the femur and

processed into slides. The frequency of polychromatic erythrocytes and reticulocytes was determined.

RESULTS

No evidence of an increased frequency of bone marrow micronucleated erythrocytes in the drug treated groups was noted. This suggests that the compound is not mutagenic. This study is acceptable for its intended purpose.

Absorption, Distribution, Metabolism And Excretion Studies

1)This information was translated from the article published in Japanese, Metabolic Fate of Amlexanox (AA-673), A New Antiallergic Agent, In Rats, Mice, Guinea-Pigs And Dogs, Japanese Pharmacology & Therapeutics 13: 4933-4954.

Laboratory: [ ]

Animal Strain: male and female Jcl:Wistar rats
male Jcl:ICR mice
male Crj:Hartley guinea-pigs
male beagle dogs [ ]

Formulation: The drug was labelled with ^{14}C in the pyridine ring and had a radiochemical purity of greater than 99%. The 14C-AA-673 was appropriately diluted with nonlabelled drug and was suspended in 5% gum arabic solution for oral administration or was dissolved in a minimum volume of 1N NaOH and diluted with phosphate buffered saline for intravenous injection. The animals were dosed at the rate of 10 mg/kg.

Absorption and Kinetics

The ratio of radioactivity in urine was calculated following oral gavage and intravenous dosing to rats, mice, guinea-pigs and dogs (fasted or fed). Bioavailability was estimated to be 46, 61, 76 and 47% in rats, mice, guinea-pigs and dogs, respectively. The site of absorption was studied in pyloric-ligated rats after intragastric or intraduodenal administration of the drug. The plasma concentration was significantly higher after intraduodenal administration suggesting the drug was absorbed mainly from the small intestine. Further studies using a jejunal loop indicated absorption was mainly by the portal route in this area. The use of thoracic duct fistulated rats given the drug orally indicated absorption was unlikely by the lymphatic route.

The absorption of the drug after oral gavage was rapid in the rat, mouse and dog. It was delayed in the guinea-pig probably due to absorption from a wide range of the intestine.

The level of ^{14}C AA-673 and its metabolites in plasma were studied for at least 24 hours following oral gavage in rats, mice, guinea-pigs and dogs. The plasma concentration of the labelled drug and its metabolites were about equal in mice, guinea-pigs and dogs suggesting the metabolic characteristics are about the same. The rat had a substantial quantity of metabolite in the plasma which was identified as a conjugate that was not noted in the other species. The composition of the metabolites from the plasma of man resembles that found in mice, guinea-pigs and dogs but not rats.

In man a single oral application of 5mg from 5% paste resulted in an area under the curve(AUC, 0 to 24 hours) of 0.36 ug.hr/ml. Ten mg/kg given intraduodenally to the rat resulted in an AUC (0 to infinity) of 4.23 ug.hr/ml. Ten mg/kg oral doses to the mouse and dog gave AUC (0 to infinity) values of 9.67 and 8.56 ug.hr/ml respectively.

Protein Binding And Erythrocyte Distribution

In vitro studies indicated radiolabelled drug was bound to plasma protein to the extent of 96 to 99% in mice, rats, guinea-pigs and dogs. The three concentrations of drug tested (0.5, 5.0 and 50 ug/ml were in the concentration range found in plasma from the oral gavage studies) indicated no dependence of binding on concentration. The binding was further studied and found to be reversible.

The percentage of drug bound or stuck to erythrocytes from these four species varied from 6 to 23% using the same drug concentration in another in vitro experiment. There did not appear to be a dependence of binding upon concentration.

Tissue Distribution And Accumulation Studies

Rats were dosed by oral gavage 1 x day for up to five days and their tissues examined for accumulation of radioactivity. No tissue accumulation of radioactivity was noted except in the organs responsible for the excretion of the drug and its metabolites. Rats were given the labelled drug intradudonally and killed at varying times up to 24 hours post dosing. Whole body autoradiography, also did not indicate any tissue accumulation other than those involved in the excretion of the drug over the 24 hour study period. These results agreed with those of the tissue distribution studies.

On day 20 of gestation rats were orally dosed with ^{14}C AA-673. Fetuses were removed from 15 minutes to 8 hours post dosing for analysis. Radioactivity was detected in the fetus and amniotic fluid indicating transfer or drug/metabolites across the placenta. There did not appear to be concentration of the drug or metabolites in the fetus since the concentration at each of the sampling times was lower than the concentration in the maternal plasma. Lacteal secretion was examined at the same times in females dosed orally with labelled drug on day 14/15 after

parturition. Radioactivity was secreted in the milk. The predominant component was unchanged drug. The concentration in milk was higher than that in plasma as time progressed.

Enzyme Induction

The ability of AA-673 to cause enzyme induction was studied. Rats were orally dosed with 0, 10, 30 or 100 mg/kg/day for a total of 7 days and the activity of hepatic microsomal enzymes was studied 24 hours after the last dose. There was no increase in liver weight, microsomal protein per gram of liver, enzymatic activity per mg protein, and microsomal content of cytochromes p450 and b5 were the same for the AA-673 treated animals vs the controls. The positive control material, phenobarbital, caused significant increases in weight of the liver, microsomal protein, all of the enzymatic activities and the microsomal content of both cytochromes. AA-673 did not cause hepatic microsomal enzyme induction in rats.

Metabolism

The metabolites in the urine and feces were identified after oral administration of the radiolabelled drug to rats, mice, guinea-pigs and dogs. In the plasma and excreta of all four species the drug was metabolized by hydroxylation and oxidation of the isopropyl moiety. The drug was metabolized by conjugation with glucuronic acid only in the rat (major) and guinea-pig (minor). Amlexanox (major fecal component) and the hydroxylated derivative (major urine metabolite) were present in the urine and feces from all four species. Unchanged amlexanox and the hydroxylated derivative have been found in the serum and urine of man after oral administration of the unlabelled drug. The urinary metabolic profiles were qualitatively similar for all species.

An in vitro study with rat tissue slices of brain, heart, lung, liver, kidney and duodenum was conducted with labelled drug to investigate the metabolism. It was determined that the conjugation was carried out mainly in the intestinal mucosa and the hydroxylation and oxidation of the isopropyl moiety were in the liver and kidney. Glucuronidation was only carried out in the rat.

Excretion

After oral administration of the labelled drug, almost all of the radioactivity was eliminated within 48 hours in rats, mice and dogs and within 120 hours in guinea-pigs. The bulk of the radioactivity appeared in the feces (75 to 91%) rather than the urine (5 to 23%).

Rats were given an oral dose of labelled drug 1 x day for 5 days and various pharmacokinetic parameters were determined. The results of this multiple dose study indicated no accumulation of either the parent drug or its metabolites during the five day study.

Summary: The drug is well absorbed from the intestine of rats, mice, guinea-pigs and dogs. It is distributed widely in tissues with no accumulation and is metabolized. The drug and its metabolites are preferentially eliminated from the body by fecal excretion and secondarily by the urinary route. AA-673 does not cause hepatic enzyme induction. These studies are acceptable for their intended purpose.

2) Pharmacokinetics And Metabolism of Amlexanox (AA-673), A New Antiallergic Agent, After Nasal Administration To Rats (Report # A-16-525; a two page report was provided)

Laboratory: [ ]

Study Design: Rats were given a single 0.25 mg/kg nasal dose of ^{14}C-AA-673 and sequential blood samples were obtained as well as feces and urine over the 24 hour study period. Animals were subjected to whole body autoradiography.

RESULTS

The ^{14}C-AA-673 was rapidly absorbed with a Tmax of 5 minutes followed by a biphasic decline. Whole body autoradiography indicated the radioactivity to be widely distributed in tissues. Excretion patterns indicated rapid elimination within 48 hours with 36 and 67% of the dose appearing in the urine and feces respectively. Analysis of the metabolites indicated that glucuronidation and oxidation of the isopropyl group occurred. This metabolic pattern is similar to the one after oral administration.

Summary: Absorption after nasal dosing is rapid. The drug does not appear to accumulate in tissues and is rapidly eliminated in the feces and urine. This study is acceptable for its intended use.

3) Intraocular Penetration of AA-673 Ophthalmic Solution, An Antiallergic Agent (Report # AA-673/S-DK02)

Laboratory: [ ]

Number of animals: total of 39 used in groups of 3 to 6

Animal Strain: Japan White Rabbit; males

Dose Level: 50 ul of a 0.25% ophthalmic solution of drug was instilled into both eyes

Route: Instillation into the conjunctival sac of the eye

Study Design: The animals were dosed and approximately 4 mL of blood was taken at the following times- 20 and 40 minutes and 1, 2, 4, 6, 8, 24 and 48 hours after instillation. Immediately after the collection of blood the animal was sacrificed. The eyeball together with the conjunctivae and extraocular muscle was removed. The conjunctivae was removed and a sample of anterior chamber aqueous was collected. The eyeball was quick frozen and cut into anterior and posterior segments. The lens, vitreous body, retina, choroid and iris and ciliary body were removed. All the tissues including blood were assayed using high pressure liquid chromatography after preparation.

RESULTS

The maximum concentration in the blood was reached in 20 minutes and then it declined thereafter. The concentration time course in each ocular tissue showed that after reaching their respective peaks, the concentrations declined exponentially and then slowly after 24 hours in the cornea and after 8 hours in the conjunctivae and anterior sclera. Only a low concentration was found in the retina and choroid up to 2 hours post instillation. After 8 hours the concentration was below the limit of detection in these tissues.

Summary: AA-673 penetrates into the cornea and conjunctivae rapidly after instillation and then disappears slowly. The drug would be expected to show sustained efficacy toward diseases of the external segment of the eye.

Summary:

Amlexanox was not a sensitizer and did not cause irritation of the mucous membrane of the mouth in a 7 day hamster cheek pouch irritatioin study. In a 6 month oral rat and dog evaluation the no effect level was 100 and 30 mg/kg respectively for hepatotoxicity which was considered to be the target organ. This was shown to be reversible in the dog in a recovery study. Life time studies giving the drug by the dietary route in the rat and mouse indicated the drug was not carcinogenic. This is indicated on the label. The no effect level in the mouse study was 30 mg/kg for toxic nephrosis and in the rat study was 80 mg/kg for biliary changes- cystic dilation, calculus formation, inflamation of the extrahepatic bile duct, cholangitis and pericholangitis. No adverse effect was noted in fertility and general reproductive performance studies in the rat, teratology studies in the rat and rabbit and peri and post-natal studies in the rat up to a 300 mg/kg dose given orally. Amlexanox was not mutagenic in the Ames or mouse micronucleus test.

The mean mg of Amlexanox per patient per day is approximately 0.2 mg/kg/day for a 60 kg person (see attachment from Chemex dated June 14, 1995). No adverse effect was noted on general reproductive performance and fertility in rat and rabbit studies up to 300 mg/kg amlexanox. This would give a no effect level of approximately 1500 times the projected human dose, which is indicated on the label.

Appears This Way
On Original

Absorption studies in the rat, mouse, guinea-pig and dog indicated the oral bioavailability to be about 50%. The intestine was the major site of absorption. The metabolic characteristics of the drug in plasma were about the same in the rat, mouse, guinea-pig and dog as they were in man following an oral dose. The rat was the only species that conjugated the material. The drug was highly bound to plasma proteins and there was no dependence of binding on the drug concentration. ^{14}C studies demonstrated no specific tissue accumulation (following a single or multiple doses) except in the organs responsible for excretion of the compound and its metabolites. The drug crossed the placental barrier and resided in the milk of lactating dams. Amlexanox was not a hepatic enzyme inducer. In the rat, mouse, guinea-pig, dog and man after oral dosing amlexanox was present in the feces (major component) and the urine(hydroxylated metabolite, minor component). After oral administration of the radiolabelled drug almost all of it was eliminated within 120 hours in rats, mice, guinea-pigs and dogs.

Conclusion:

The use of amlexanox for the treatment of aphthous ulcers on the oral mucosa as proposed would appear to be safe with respect to the results of the preclinical animals studies.

RECOMMENDATIONS

The question of projected human daily dose and the addition of wording to the package insert to instruct the patient as to what constitutes a dab-i.e. appropriate dose/ulcer was answered on June 14, 1995 by Dr. M. Charney. This NDA is approvable from the preclinical standpoint.

John Wedig, Ph.D.
Toxicologist

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Norman See
8/2/04 01:29:43 PM
PHARMACOLOGIST

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-727

Statistical Review(s)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	21-727/N000	
Drug Name:	OraDisc™ (Amlexanox 2 mg mucoadhesive patch)	
Indication(s):	Recurrent minor aphthous ulcer	
Applicant:	Access Pharmaceuticals, Inc.	
Dates:	Submitted:	December 4, 2003
	Received:	December 9, 2003
	User fee:	October 9, 2004
	Review completion:	July 16, 2004
Review Status:	Standard	
Biometrics Division:	Division of Biometrics III (HFD-725)	
Statistics Reviewer:	Shiowjen Lee, Ph.D.	
Concurring Reviewers:	Mohamed Alosh, Ph.D.	
Medical Division:	Dermatologic and Dental Drug Products (HFD-540)	
Clinical Team:	Fred Hyman, DDS, M.P.H.	
Project Manager:	Jacquelyn Smith	

Keywords: aphthous ulcer, complete ulcer healing, complete resolution of pain, anti-inflammatory, analgesic, superiority and non-inferiority.

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

One pivotal trial (AP-C-1U106, denoted as study 1U106) and one supportive trial (AP-C-9E03, denoted as study 9E03) were evaluated for the efficacy claim of OraDisc™ (amlexanox 2 mg) mucoadhesive patch in the treatment of recurrent mild aphthous ulcer. The overall superiority of OraDisc™ to vehicle patch is established with respect to the primary efficacy endpoint, the percentage of patients with complete healing of all treated ulcers on Day 5, based on the results in study 1U106. This finding is further supported based on the results in study 9E03. However, OraDisc™ is not shown statistically to have efficacy benefits over no-treatment in study 1U106 in regard to the primary efficacy endpoint. The superiority of OraDisc™ to vehicle patch is not established with respect to the secondary efficacy endpoints, measured in terms of the percentage of patients with complete resolution of pain on Day 5, and the time to complete resolution of pain in both studies 1U106 and 9E03.

Safety results from studies 1U106 and 9E03 in terms of the incidence of adverse events generally suggest that the safety profile of OraDisc™ is comparable to vehicle patch.

1.2 Brief Overview of Clinical Studies

The study drug product is OraDisc™ (amlexanox 2 mg mucoadhesive patch). It is indicated for the treatment [ ] aphthous ulcer 4 times daily (after each meals and before bedtime) for up to 7 days or till ulcers are healed, whichever occurs first.

For establishing efficacy claim of OraDisc™, one pivotal trial 1U106 and one supportive trial 9E03 were conducted during June 2002 – March 2003 and June 2000 – December 2000, respectively. It should be noted that study 1U106 used the final formulation to-be-marketed in the trial; while study 9E03 used the early formulation of the study drug. Both formulations have the active ingredient of amlexanox 2 mg. Totals of 701 and 401 patients who were 12 years of age and older and had at least one ulcer treated at baseline were enrolled from 26 and 18 study sites for studies 1U106 and 9E03, respectively. The enrolled patients were randomized in a ratio of 3:3:1 to receive amlexanox patch, vehicle patch and no-treatment in study 1U106; while an allocation ratio of 2:2:1 was applied to the respective group in study 9E03. The randomization resulted in 303, 301 and 97 patients in each treatment group, respectively, for study 1U106; while 157, 163 and 81 patients for study 9E03. The treatment duration was 7-day and the primary time point for efficacy assessment was on Day 5.

1.3 Statistical Issues and Findings

Statistical Issues

Even though the Division's recommendation on a "win" for a clinical trial (EOP-2 Meeting dated 8/20/01) were

- Active should be superior to vehicle, and
- Vehicle should be non-inferior to no-treatment

the comparison between amlexanox and no-treatment in study 1U106 is non-significant with respect to the primary efficacy endpoint (p-value = 0.093 and 0.088 based on CMH test adjusted

for center and logistic regression method on the ITT population, respectively). This comparison was examined to ensure the efficacy benefit of amlexanox following the fact that the overall non-inferiority of vehicle to no-treatment was not established with respect to the pre-specified margin of 8%, however, the limit was close to the margin. The non-significant results between amlexanox and no-treatment could be attributed to the following factors:

1. The treatment allocation ratio for amlexanox vs. no-treatment was 3:1. The superiority of amlexanox to no-treatment is not established due to a smaller sample size for the no-treatment arm even though the ulcer healing rate for the no-treatment group is similar to that of vehicle patch (21.6% vs. 21.9%).
2. Even though no sample size calculation was considered for the comparison of amlexanox vs. no-treatment at the design stage, the planned sample size along with the assumptions in the sample size calculations would warrant at least an 80% power to demonstrate the superiority of amlexanox over no-treatment. However, the actual response rates in study 1U106 are lower than those of the assumptions. The treatment difference (δ) is 20% based on the assumptions, as compared to 8.7% from the results in study 1U106.

For study 9E03 to be supportive, one statistical issue is that seven investigators participated in both studies 1U106 and 9E03. This might violate the independence of clinical studies for establishing efficacy. The seven common investigators [

] The patient enrollment for these investigators accounted for 27.4% (192/701) and 49.6% (199/401) of the total enrollment in studies 1U106 and 9E03, respectively.

A sensitivity analysis was conducted to examine the impact of the seven common investigators on the efficacy results. Results are presented in the section of statistical findings.

Statistical Findings

The sponsor in this submission presented results of pivotal study 1U106 and supportive study 9E03 in support of the efficacy and safety claim of OraDisc™ (amlexanox patch 2 mg) for the treatment of [ ] aphthous ulcers. The dosing of OraDisc™ is one patch per ulcer four times daily (after each meal and before bedtime) for up to 7 days or until all ulcers treated have healed, whichever occurs first. The primary efficacy endpoint is the percentage of patients with complete healing of all treated ulcers on Day 5.

Efficacy results based on the ITT population with imputing missing data as "not healed" are presented in Table S.1 for studies 1U106 and 9E03. As up to 3 ulcers per patient were treated in study 1U106 as compared to only one treated ulcer per patient in study 9E03, efficacy results of the complete ulcer healing for study 9E03 and subgroup results over the number of treated ulcers at baseline for study 1U106 are presented in Table S.2.

The following summarizes the results.

Efficacy:

Primary efficacy endpoint –

- Overall, amlexanox is superior to vehicle in study 1U106 (p-value = 0.015, Table S.1). This finding is further supported based on the results in study 9E03 (p-value = 0.026, Table S.1). The overall ulcer healing rates are 30.4% vs. 21.9% for amlexanox vs. vehicle in study 1U106; and 48.4% vs. 35.6% in study 9E03.
- The non-inferiority evaluation of vehicle patch to the no-treatment arm is not established for study 1U106. The lower limit of the one-sided 97.5% confidence interval –9.2% is outside the pre-specified non-inferiority margin of –8%. On the other hand, the non-inferiority of vehicle patch to the no-treatment arm is established in study 9E03 (Table S.1).
- To ensure efficacy benefit of amlexanox, the comparison between amlexanox and the no-treatment arm was examined. The overall superiority of amlexanox to no-treatment is not established for study 1U106 (p-value = 0.093, Table S.1). However, the superiority of amlexanox to no-treatment is established for study 9E03 (p-value = 0.005, Table S.1).
- For 3 treated ulcers, amlexanox was numerically worse than vehicle and no-treatment groups in study 1U106 (Table S.2) with respect to the primary efficacy endpoint. The ulcer healing rates were 7.7% vs. 15.0% vs. 12.5% for amlexanox vs. vehicle vs. no-treatment. As this category of patients accounted for about 8% of the study enrollment, there may be insufficient data to evaluate the labeling claim for treatment of 3 ulcers.
- Female patients did better than male patients with respect to the complete ulcer healing.

Secondary efficacy endpoints –

- In contrast to results of the primary efficacy endpoint, results from studies 1U106 and 9E03 did ***not*** show the superiority of amlexanox to vehicle in pain resolution, measured in terms of the percentage of patients with complete resolution of pain on Day 5, and time to complete resolution of pain (Table S.1). The superiority of amlexanox to no-treatment is established for complete pain resolution in both trials (Table S.1).

Others –

- There were seven common investigators participated in the two studies. Study 1U106 was conducted later than study 9E03. For the independence of the two studies, results of the primary efficacy endpoint excluding the seven sites for study 1U106 show that amlexanox is superior to vehicle (p-value = 0.037), and to no-treatment arm (p-value = 0.016); and amlexanox is non-inferior to vehicle (limit is –4.8% > –8%, Table S1).
- Vehicle patch had a numerically better (but not statistically) outcome than amlexanox in the ulcer healing rate on Day 7 for study 1U106. The ulcer healing rates on Day 7 were 50.8% vs. 52.8% for amlexanox vs. vehicle.

Safety:

The safety profile of amlexanox patch is generally comparable to vehicle patch in terms of the incidence of adverse event.

- About 12.5% vs. 14.0% of patients in amlexanox vs. vehicle groups experienced treatment-related application site adverse events in study 1U106; while about 9.6% vs. 7.4% of patients in study 9E03.
- The most frequent treatment-related application site adverse event was pain with 8.6% vs. 7.6% of patients in amlexanox vs. vehicle groups for study 1U106. The most frequent treatment-related application site events in study 9E03 were burning and pain with 4.5% and 3.8% in amlexanox arm; and 2.5% and 3.7% in vehicle group.

Note that one patient in the no-treatment group had an adverse event potentially related to the study medication (Ear/Labyrinth disorders) in study 1U106. This might be attributed to an error in reporting.

Table S.1: Efficacy Results for Studies 1U106 and 9E03

Study (duration)	Amlexanox (A)	Vehicle (V)	No-treatment (N)	Comparison	p-value or LL
Primary: percentage of patients with complete healing of all treated ulcers on Day 5					
1U106 – Overall (6/02 – 3/03)	92/303 (30.4%)	66/301 (21.9%)	21/97 (21.6%)	A vs. V[1] A vs. N[1] LL for V vs. N[2]	0.015 0.093 –9.2%
The 7 Sites	27/84 (32.1%)	18/82 (22.0%)	10/26 (38.5%)	A vs. V[1] A vs. N[1] LL for V vs. N[2]	0.148 0.540 –38.2%
Remaining Sites	65/219 (29.7%)	48/219 (21.9%)	11/71 (15.5%)	A vs. V[1] A vs. N[1] LL for V vs. N[2]	0.037 0.016 –4.8%
9E03 (6/00 – 12/00)	76/157 (48.4%)	58/163 (35.6%)	23/81 (28.4%)	A vs. V[1] A vs. N[1] LL for V vs. N[2]	0.026 0.005 –5.6%
Secondary: Percentage of patients with complete resolution of pain on Day 5					
1U106	134/303 (44.2%)	132/301 (43.9%)	30/97 (30.9%)	A vs. V[1] A vs. N[1]	0.988 0.018
9E03	94/157 (59.9%)	90/163 (55.2%)	32/81 (39.5%)	A vs. V[1] A vs. N[1]	0.409 0.002
Secondary: time (in days) to complete resolution of pain					
1U106	5.0	5.0	6.0	A vs. V[3] A vs. N[3]	0.704 0.034
9E03	4.0	4.0	5.5	A vs. V[3] A vs. N[3]	0.283 0.002

[1] Comparisons of A vs. V (Amlexanox vs. vehicle) and A vs. N (Amlexanox vs. no-treatment) are based on CMH test adjusting for study site.
[2] Comparison of V vs. N (vehicle vs. no-treatment) is based on the lower limit of one-sided 97.5% confidence interval for (Vehicle – No-treatment). LL represents the exact lower limit of one-sided 97.5% confidence interval computed using StatXact version 5.
[3] Comparisons are based on log-rank test.

Table S.2: Percentage of Patients with Complete Ulcer Healing on Day 5 By the Number of Treated Ulcer

ITT Analysis	Amlexanox	Vehicle	No-treatment
Study 1U106			
Overall, n (%)	92/303 (30.4%)	66/301 (21.9%)	21/97 (21.6%)
One treated ulcer	80/219 (36.5%)	59/231 (25.5%)	19/68 (27.9%)
Two treated ulcers	10/58 (17.2%)	4/50 (8.0%)	1/21 (4.8%)
Three treated ulcers	2/26 (7.7%)	3/20 (15.0%)	1/8 (12.5%)
Study 9E03			
Overall, n(%)	76/157 (48.4%)	58/163 (35.6%)	23/81 (28.4%)

2. INTRODUCTION

2.1 Overview

Aphthasol (Amlexanox Oral Paste) 5% Topical was approved on December 17, 1996 in the U.S. (NDA 20-511) for the treatment of signs and symptoms of emerging and existing aphthous ulcers in patients with normal immune systems. Amlexanox is marketed in Japan as oral tablets (25 and 50 mg) for the treatment of bronchial asthma (approved in 1987) and allergic rhinitis (approved 1988). A 0.25% ophthalmic solution with active ingredient of amlexanox is also marketed in Japan for allergic conjunctivitis (approved in 1989). Sponsor's current proposed drug product, OraDisc™, is a new formulation of amlexanox. It is a multi-layer erodible and mucoadhesive patch, 0.5-inch in diameter, containing 2 mg of amlexanox. According to the sponsor, the formulation is developed to provide a more targeted release of amlexanox to the ulcerated area. The indication is for the treatment of [redacted] aphthous ulcer. The proposed dosing regimen is 2 mg per patch 4 times daily (after meals and before bedtime) for up to 7 days, or till ulcers are healed, whichever occurs first.

Three clinical studies are submitted in the NDA for the efficacy claim of OraDisc™:

- Study AP-C-1U106 (denoted as study 1U106) was conducted in the U.S. based on the final formulation to-be-marketed.
- Study AP-C-9E03 (denoted as study 9E03) was conducted in the U.S. and Northern Ireland based on the early formulation.
- Study AP-C-9E02 (denoted as study 9E02) was conducted in the United Kingdom (U.K.) based on the early formulation.

The overview of the three clinical studies is presented in Table 1.

Table 1: Overview of Clinical Studies

Study	Study conducted Country (date)	Patients inclusion	Treatment arms – n	Comments on treatments
Phase 2/3 study				
9E02	United Kingdom (2/21/00 – 5/31/01)	Patients who were 18 years of age and older with recurrent aphthous ulcers.	Amlexanox – 26 Vehicle – 26	The study drug amlexanox was the early formulation. The study was a single center trial and study duration was 3-day.
9E03	17 U.S. centers and 1 Northern Ireland center (6/28/00 – 12/15/00)	Patients who were 12 years of age and older with recurrent aphthous ulcers taking 5 days or more to resolve.	Amlexanox – 157 Vehicle – 163 No-treatment – 81	The study drug amlexanox was the early formulation. The study duration was 7-day.
Phase 3 – pivotal study				
1U106	26 U.S. centers (6/3/02 – 3/23/03)	Patients at least 12 years of age with recurrent minor aphthous ulcers taking 5 days or more to resolve.	Amlexanox – 303 Vehicle – 301 No-treatment – 97	The study drug amlexanox was the final formulation to-be-marketed. The study duration was 7-day.

Study 1U106 was conducted in 26 U.S. study sites during June 2002 and March 2003. It is the designated single Phase 3 pivotal trial studying the final formulation to-be-marketed. A total of

701 patients were enrolled and randomized in a ratio of 3:3:1 to amlexanox, vehicle and no-treatment groups, respectively. Up to 3 ulcers were treated per patient. The primary objective was to evaluate the efficacy and safety of amlexanox patch in the healing of ulcers as compared to vehicle patch. It should be noted that in order to demonstrate that the vehicle patch did not have a worsening and irritating effect on the ulcers, the no-treatment arm was included in the study design. This was in agreement with the Division at the End-of-Phase 2 (EOP-2) Meeting dated 8/20/01.

Study 9E02 was conducted in the U.K. during February 2000 and May 2001. It was designed as double blind, vehicle controlled, single center and randomized. The objective was to determine the effect of amlexanox on the prevention of recurrent aphthous ulcers in patients presenting at the prodromal stage. The study duration was 3-day. On the other hand, study 9E03 was conducted in 17 U.S. centers and 1 Northern Ireland center during June 2000 and December 2000. The study design was similar to that of study 1U106 except that only one ulcer was treated per patient. A total of 401 patients were enrolled and randomized in a ratio of 2:2:1 to amlexanox, vehicle and no-treatment groups, respectively. The dosing was 2 mg per patch 4 times daily for up to 7 days or till ulcer was healed. It, however, should be noted that OraDisc™ in studies 9E02 and 9E03 was the early formulation, which is different from the final formulation to-be-marketed.

To address drug efficacy within the claimed duration of 7 days, this statistical review will primarily focus on the Phase 3 pivotal study 1U106. As the final and the early formulations have the same active ingredient of amlexanox 2 mg, study 9E03 is reviewed as supportive. Study 9E02 is not reviewed, as it was designed as single-center with study duration of 3-day.

2.2 Data Sources

The data summary in this review is based on the sponsor's NDA submission Volumes 1.1-1.33 dated 12/04/03, received by the Center dated 12/09/03, sponsor's responses to the 74-Day Filing Review Letter dated 3/15/04, sponsor's responses to the Division's information request dated 3/24/04, and electronic submission dated 1/30/04 in the Electronic Document Room location of \\cdsesub1\n21727\n_000.

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Pivotal Study 1U106

Study Design

Study 1U106 was designed as multi-center (26 U.S. centers), evaluator-blind, vehicle-, and no-treatment controlled, and randomized. It was conducted during June 2002 and March 2003. The study objective was to determine the effect of amlexanox OraDisc™ on the healing rate of recurrent aphthous ulcers and its safety profile as compared to vehicle patch. Patients studied were those who were at least 12 years of age and had recurrent aphthous ulcers. For study participation, patients were asked to present to the study site within 36 hours after the formation of aphthous ulcers following the screening visit for study eligibility. Once the ulcers were

confirmed by study site investigator, the patients were then randomized in a ratio of 3:3:1 to receive amlexanox patch, vehicle patch, or no-treatment, respectively, according to the randomization list generated prior to the start of the study. Up to 3 ulcers were treated per patient. Patients treated ulcers four times daily by applying the mucoadhesive patch(es) to the ulcer(s) and allowing it to dissolve in the mouth. Treatment continued for 7 days or until all ulcers treated have healed, whichever occurred first. A total of 701 patients were enrolled. The treatment randomization resulted in 303, 301 and 97 subjects in amlexanox, vehicle and no-treatment groups, respectively.

No-treatment arm was included in the study design in order to demonstrate that vehicle patch did not have worsening and irritating effect on the treated ulcers. Per EOP-2 meeting minutes (dated 8/20/01), the criteria for a successful trial were,

- Amlexanox is superior to its vehicle, and
- Vehicle is non-inferior to no-treatment arm.

To establish the non-inferiority of vehicle patch to the no-treatment arm, the non-inferiority margin of 8% was proposed and in agreement with the Division with respect to the percentage of patients with complete healing of all treated ulcers (per Special Protocol Assessment submitted on 12/20/01).

The efficacy evaluation included investigator measurements of the size of treated ulcer(s) (diameter 1 x diameter 2) in mm^2 scheduled on Days 1, 3, 4, 5, 6 and 7, and twice-daily subject records of oral pain on a 100-mm visual analog scale (VAS). For data analyses, the VAS score was dichotomized into < 5 mm (no pain) and ≥ 5 mm (pain).

Randomization and Blinding

Sponsor's document indicated that the study randomization list was generated using [ ] in February 2000 based on blocks of size 7. A total of 114 blocks of treatment assignment were generated. The first patient was enrolled on 6/3/2002. The clinical supplies were shipped to the study sites in blocks of 7, 14 or 21, as needed. Following examining their randomization list along with date of patient enrollment, one patient (ID 666) at study site 162 was randomized out of sequence, prior to patients 664 and 665. However, this is not expected to have an impact on the efficacy results.

The study was designed as evaluator-blind. According to the sponsor, amlexanox patch and vehicle patch were considered blinded based on appearance, taste, sensation on the oral mucosa and similar expected side-effect profiles. However, patients assigned to the no-treatment group were not blinded to their treatment assignment. To ensure that the ulcer evaluation remained blinded for all treatment groups, the investigators performing the evaluation had no access to the clinical supplies, nor did they have access to patient's diary during the trial.

Efficacy Endpoints Specified in the Protocol and Submission

The following endpoints were pre-specified in the sponsor's protocol and agreed upon with the Division.

- Primary efficacy endpoint was the percentage of patients with all treated ulcers healed (ulcer size of 0 mm^2) on Day 5.
- Secondary efficacy endpoints included

a. Time to ulcer healing, which was defined as the number of days until healing if the ulcer healed on or before Day 7, or as a right-censored observation if the ulcer did not heal on or before Day 7.
b. Percentage of patients with complete resolution of pain on Day 5, where complete resolution of pain is defined as pain score < 5 mm on a 100-mm VAS scale.
c. Time to healing based on the complete resolution of pain.

Sponsor's safety evaluation was mainly the incidence of adverse events, severity and relationship of adverse events. Adverse events were also categorized as either "application site reaction" or "events other than application site reaction".

Population Analyzed in the Protocol and Submission

For efficacy evaluation, the intent-to-treat (ITT) and efficacy evaluable populations were analyzed with the ITT analysis as the primary. Sponsor's ITT population included all randomized subjects whether or not they ingested one dose of study medication. The efficacy evaluable population was defined per protocol as patients who:

- Completed follow-up through healing of the treated ulcer(s) or through Day 7 if the treated ulcer(s) did not heal prior to Day 7;
- Did not use analgesic (oral or topical) or other aphthous ulcer treatments during the trial;
- Were compliant with study visit schedule and did not miss more than one visit.

Sponsor's safety population included all randomized patients who took at least 1 dose of study medication and all the patients in the no-treatment group.

Statistical Analysis Plan in the Protocol and Submission

The following statistical methods for efficacy analysis were pre-specified in the sponsor's protocol and agreed upon with the Division at EOP-2 Meeting (dated 8/20/01) and 45-Day Special Protocol Assessment submission (dated 12/20/01).

- Cochran-Mantel-Haenszel (CMH) test adjusting for investigator was proposed as the primary analysis method to test the difference among three treatment groups. If the overall treatment effect was significant, the following pairwise comparisons were made:
  b. Testing the difference between amlexanox and vehicle.
  c. Calculating one-sided 97.5% confidence interval for the difference in ulcer complete healing rate for vehicle patch versus no-treatment (i.e. Vehicle – No-treatment). The non-inferiority of vehicle to the no-treatment group is established if the lower limit of the one-sided 97.5% confidence interval is no less than –8%.

  A logistic regression analysis with terms of treatment, investigator, and treatment-by-investigator was proposed as the secondary analysis to analyze the healing rate. They indicated baseline assessment such as number of ulcers at baseline or baseline ulcer size would be included in the model as a covariate if it showed a strong imbalance between treatment groups.
- Kaplan-Meier method was proposed to estimate time to healing (based on ulcer size of 0 mm^2 or complete pain resolution). Log-rank test and Wilcoxon test were proposed to compare the survival curves between amlexanox and vehicle arms.
- The percentage of patients with complete resolution of pain was analyzed in the same manner as the primary efficacy endpoint.

- For missing data handling, any data missing before the subject healed or after a subject withdrew, for any reason other than complete healing, were imputed as "not healed".
- For small sites pooling, the investigators with fewer than 20 subjects were to be combined with other investigators for analysis to achieve total enrollments of at least 28 subjects. There were 11 investigators had each enrolled less than 20 subjects. These 11 investigators were pooled based on geographical location into 3 centers:
  – Center 997 (Central US): investigators 125, 132, 163, 182, and 172 (41 patients in total)
  – Center 998 (Western US): investigators 183 and 177 (30 patients in total)
  – Center 999 (Eastern US): investigators 166, 168, 171 and 181 (28 patients in total)

Multiplicity Adjustment
For efficacy claim, the trial needs to demonstrate that (1) amlexanox is superior to vehicle, and (2) vehicle is non-inferior to the no-treatment arm. Consequently, no multiplicity adjustment is needed.

Reviewer's Comments on Study 1U106:

1. For the analysis of the complete ulcer healing rate, sponsor's results based on the logistic regression in the NDA submission are not justified for the following reason:
   - Sponsor's protocol (dated 3/6/02) stated that logistic regression with terms of treatment, investigator and treatment-by-investigator interaction would be used. They stated in the protocol that if any baseline measurements show a strong imbalance between treatment groups, that baseline variable would be included as a covariate in the model. However, the sponsor's logistic regression analyses included baseline ulcer size as a covariate even though the baseline ulcer size is not significantly different among the three treatment groups (see Table A.2 of the Appendix).

   Consequently, the primary analysis based on the CMH test adjusting for study site is the focus in this review. As supportive, analyses based on the logistic regression are performed by the reviewer. The logistic regression model includes terms of treatment, investigator and treatment-by-investigator interaction.

3.1.1.1 Patient Disposition and Baseline Characteristics

To evaluate the comparability between treatments, Table 2 presents results of patient disposition. The patient enrollment by investigator and patient demographics and baseline characteristics are presented in Tables A.1 and A.2 of the Appendix, respectively.

Generally, treatment groups are comparable with respect to the ITT, efficacy-evaluable and safety populations (Table 2). About 93.7%, 96.3% and 91.8% of patients completed the study in amlexanox, vehicle and no-treatment groups, respectively. A high proportion of patients withdrew from the study due to patient's request (17 out of 38). No other significant discrepancies are noted.

For demographics and baseline characteristics, three treatment arms are generally comparable. The study enrolled about 12%, 16.3% and 12% pediatric patients in amlexanox, vehicle and no-treatment group, respectively. There is no significant difference among treatment groups in mean age (p-value = 0.66, Table A.2 of the Appendix). About 65% of enrolled patients are females. Most enrolled patients are Caucasian (87.5%, 86.0% and 79.4% in the respective group). The majority of the enrolled patients (at least 70%) had 1 ulcer treated. About 8% of the patients had

3 treated ulcers. No outstanding difference is noted for each of demographic and baseline characteristics listed (Table A.2 of the Appendix).

Table 2: Patient Disposition – Study 1U106

Subjects	Amlexanox	Vehicle	No-treatment	Overall
Subject Enrolled	303	301	97	701
Completed study	284 (93.7%)	290 (96.3%)	89 (91.8%)	663 (94.6%)
ITT population	303 (100%)	301 (100%)	97 (100%)	701 (100%)
Discontinued, total	19 (6.3%)	11 (3.7%)	8 (8.2%)	38 (5.4%)
Worsening of condition	2 (0.7%)	0	0	2 (0.3%)
Adverse event	0	4 (1.3%)	0	4 (0.6%)
Patient's request	8 (2.6%)	2 (0.7%)	7 (7.2%)	17 (2.4%)
Protocol violation	3 (1.0%)	2 (0.7%)	0	5 (0.7%)
Lost to follow-up	4 (1.3%)	1 (0.3%)	1 (1.0%)	6 (0.9%)
Other reason	2 (0.7%)	2 (0.7%)	0	4 (0.6%)
Efficacy evaluable population	278 (91.7%)	276 (91.7%)	85 (87.6%)	639 (91.2%)
Safety population	303 (100%)	301 (100%)	97 (100%)	701 (100%)

Source: Sponsor's NDA submission (Module 5, Vol.1.3, page 47).

3.1.1.2 Primary Efficacy Endpoint

The primary efficacy endpoint is the percentage of patients with complete healing of all treated ulcers on Day 5. The criteria for successful pairwise comparisons are:
(1) Amlexanox is superior to vehicle; and
(2) Vehicle is non-inferior to the no-treatment arm with a non-inferiority margin of 8%.
Table 3 presents the efficacy results.

Table 3: Percentage of Patients with Complete Healing of All Treated Ulcers on Day 5 – Study 1U106

Analysis	Amlexanox	Vehicle	No-treatment
ITT	92/303 (30.4%)	66/301 (21.9%)	21/97 (21.6%)
Comparison[1]			
Amlexanox vs. Vehicle	0.015		
Vehicle vs. No-treatment	–9.2%		
Efficacy-Evaluable	90/278 (32.4%)	65/276 (23.6%)	20/85 (23.5%)
Comparison[1]			
Amlexanox vs. Vehicle	0.027		
Vehicle vs. No-treatment	–10.3%		

Source: Sponsor's NDA submission (Module 5, Vol.1.3, pages 61-62, 132-133 and 140-141).
[1] The comparison (p-value) between amlexanox and vehicle was based on CMH test adjusting for investigator. The listing for the comparison between vehicle and no-treatment was the lower limit of one-sided 97.5% confidence interval of the treatment difference (Vehicle – No-treatment).

The summary of Table 3 is:

- Point estimates based on the ITT and efficacy evaluable populations are generally consistent.
- Amlexanox is statistically superior to vehicle based on the ITT and the efficacy evaluable analyses (p-value = 0.015 and 0.027, respectively). The ITT ulcer healing rates are 30.4% vs. 21.9% for amlexanox vs. vehicle.
- However, the overall non-inferiority assessment of vehicle vs. no-treatment is not established with respect to the pre-specified margin of 8%. The lower limits of the one-sided 97.5%

confidence interval based on the ITT and efficacy evaluable populations are –9.2% and –10.3%, which are less than margin of –8%.

As supportive, analyses based on the logistic regression are performed. The model included terms of treatment, investigator, and treatment-by-investigator interaction. The interaction term was tested at a significance level of 0.10. The ITT analysis demonstrates that amlexanox is superior to vehicle with p-value of 0.014.

To ensure the efficacy benefit of amlexanox, the comparison between amlexanox and no-treatment is performed. The superiority of amlexanox patch to the no-treatment arm is not established in regard to the percentage of patients with complete healing of all treated ulcers on Day 5 (p-value = 0.093 based on CMH test adjusted for center on the ITT population). This is further confirmed using the logistic regression method with a p-value of 0.088. The non-significant results could be attributed to the following factors:

1. The treatment allocation ratio for amlexanox vs. no-treatment was 3:1. The superiority of amlexanox to no-treatment is not established due to a smaller sample size for the no-treatment arm even though the ulcer healing rate for the no-treatment group is similar to that of vehicle patch group (21.6% vs. 21.9%).
2. Even though no sample size calculation was considered for the comparison of amlexanox vs. no-treatment at the design stage, the planned sample size along with the assumptions in the sample size calculations would warrant at least an 80% power to demonstrate the superiority of amlexanox over no-treatment. However, the response rates in the current trial are lower than those of the assumptions. The treatment difference (δ) is 20% based on the assumptions, as compared to 8.7% from the results in the current trial.

Discussion:
According to the sponsor (Module 5, Vol.1.3, page 63), the reason that the overall non-inferiority of vehicle patch to the no-treatment arm was not established statistically as compared to the pre-specified margin of –8% was because of the small sample size selected for the no-treatment group. Their sample size calculation was powered based on the primary comparison of amlexanox patch vs. vehicle patch.

Reviewer's Comment:

1. Sponsor's sample size calculation in the protocol assumed response rates of 48.4%, 35.6% and 28.4% for amlexanox, vehicle and no-treatment groups, respectively, along with a non-inferiority margin of 8%.
   - The planned sample sizes of 315, 315, and 105 for the respective group in the protocol would give 90% power for the superiority comparison between amlexanox and vehicle; and 83% power for the non-inferiority assessment between vehicle and the no-treatment arm (StatXact Version 5.0).
   - Even though the actual study enrollments were 301 and 97 in vehicle and the no-treatment arms, such sample sizes would give a power of about 80% for non-inferiority comparison based on the response rates of 35.6% and 28.4% in the respective group. Therefore, the planned sample sizes at the protocol stage and the actual enrollments in the trial were ***not*** small to demonstrate the non-inferiority of vehicle patch over the no-treatment group.

2. The response rates in the current trial apparently are lower than those assumed in the sample size calculations. In particular, the response rates of vehicle patch and no-treatment arm are similar (21.9% vs. 21.6%, in Table 3) in the current trial, which are in contrast to those in the assumption for the sample size calculation (35.6% vs. 28.4%). This is the reason that the non-inferiority objective is not met as compared to the pre-specified margin of 8%.

3.1.1.3 Secondary Efficacy Endpoints

Sponsor's secondary efficacy endpoints included
a. Time to complete healing of all treated ulcers
b. Percentage of patients with complete resolution of pain on Day 5
c. Time to complete resolution of pain

Results of the secondary efficacy endpoints are presented in Tables 4.a-4.b. The summary is:
- Results based on the ITT and efficacy evaluable populations are generally consistent.
- In contrast to results of the primary efficacy endpoint, the superiority of amlexanox to vehicle is ***not*** established in all secondary endpoints.
  - Percentage of patients with complete resolution of pain – p-value = 0.988 for ITT analysis, and 0.807 for efficacy evaluable analysis (Table 4.a).
  - Time to complete healing of all treated ulcers – p-value $\geq$ 0.344 for the ITT analysis and $\geq$ 0.395 for the efficacy evaluable analysis using log-rank and Wilcoxon tests (Table 4.b).
  - Time to complete resolution of pain – p-value $\geq$ 0.536 for the ITT analysis and p-value $\geq$ 0.514 for the efficacy evaluable analysis using log-rank and Wilcoxon tests (Table 4.b).
- In contrast to results of the primary efficacy endpoint, amlexanox is superior to the no-treatment group in terms of the percentage of patients with complete resolution of pain (p-value = 0.018 and 0.025 for the ITT and efficacy evaluable analyses, Table 4.a); and marginally superior with respect to the time to complete resolution of pain (p-value $\leq$ 0.034 and $\leq$ 0.061 for the ITT and efficacy evaluable analyses, Table 4.b). However, they are not significantly different with respect to time to complete healing of all treated ulcers, as p-value $\geq$ 0.528 and $\geq$ 0.345 for log-rank and Wilcoxon tests (Table 4.b).

Table 4.a: Percentage of Patients with Complete Resolution of Pain on Day 5 – Study 1U106

Analysis	Amlexanox	Vehicle	No-treatment
ITT	134/303 (44.2%)	132/301 (43.9%)	30/97 (30.9%)
Comparison (p-value)[1]			
Amlexanox vs. Vehicle	0.988		
Amlexanox vs. No-treatment	0.018		
Efficacy Evaluable	126/278 (45.3%)	121/276 (43.8%)	28/85 (32.9%)
Comparison (p-value)[1]			
Amlexanox vs. Vehicle	0.807		
Amlexanox vs. No-treatment	0.025		

Source: Sponsor's NDA submission (Module 5, Vol.1.3, pages 68-69, 164-169).
[1] p-value is based on CMH test adjusting for investigator.

Table 4.b: Time to Healing – Study 1U106

Treatment/Comparison	Median time to healing (in days)	Log-Rank test (p-value)	Wilcoxon test (p-value)
Time to complete healing of all treated ulcers			
ITT			
Amlexanox patch	6.0		
Vehicle patch	6.0		
No-treatment	6.0		
Comparison			
Amlexanox vs. Vehicle		0.656	0.344
Amlexanox vs. No-treatment		0.528	0.345
Efficacy Evaluable			
Amlexanox patch	6.0		
Vehicle patch	6.0		
No-treatment	6.0		
Comparison			
Amlexanox vs. Vehicle		0.712	0.395
Amlexanox vs. No-treatment		0.635	0.437
Time to complete resolution of pain score			
ITT			
Amlexanox patch	5.0		
Vehicle patch	5.0		
No-treatment	6.0		
Comparison			
Amlexanox vs. Vehicle		0.704	0.536
Amlexanox vs. No-treatment		0.034	0.016
Efficacy Evaluable			
Amlexanox patch	5.0		
Vehicle patch	5.0		
No-treatment	6.0		
Comparison			
Amlexanox vs. Vehicle		0.775	0.514
Amlexanox vs. No-treatment		0.061	0.032

Source: Sponsor's NDA submission (Module 5, Vol.1.3, pages 150-151, 174-175).

The non-significant evidence between amlexanox and vehicle in complete pain resolution can be further confirmed from the percentage of patients with complete pain resolution, and mean change of pain score from baseline over time. Results are presented in Figures 1-2. Both figures indicate that amlexanox and vehicle groups are inseparable with respect to the percentage of patients with complete pain resolution and mean change of pain score over time.

Figure 1: Percentage of Patients with Complete Resolution of Pain over Time

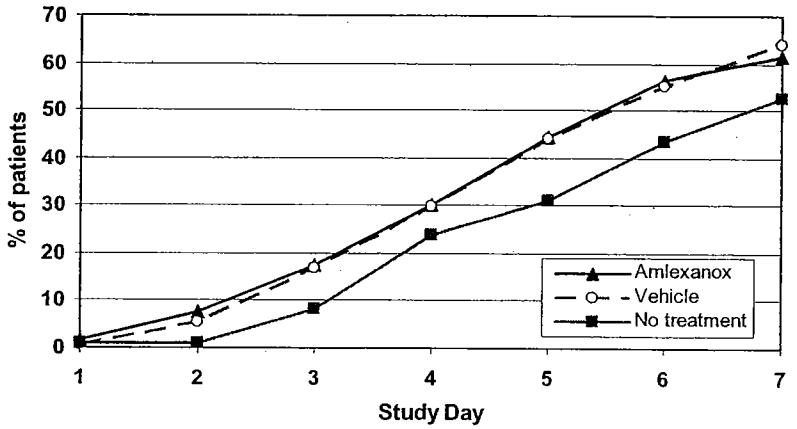
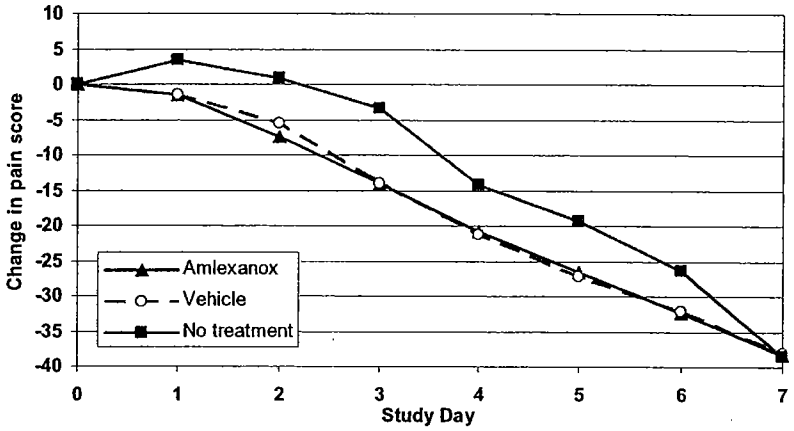


Figure 2: Mean Change of Pain Score from Baseline over Time



3.1.1.4 Effect of Missing Data Handling

Sponsor's pre-specified method of handling missing data on Day 5 was imputing missing as "not healed". To examine the robustness of the missing data handling on the primary efficacy results, missing data pattern is examined. A total of 72 (23.8%), 50 (16.6%) and 15 (15.5%) patients had missing measurements on Day 5 in amlexanox, vehicle and no-treatment arms, respectively. The reasons included having all treated ulcers healed prior to Day 5 and left the study, missed the Day 5 visit, and discontinuation from the study. Table 5 presents the missing data pattern.

Table 5: Missing Data Pattern on Day 5 – Study 1U106

Reasons for Missing Measurements on Day 5	Amlexanox (n = 303)	Vehicle (n = 301)	No-treatment (n = 97)
All treated ulcers healed prior to Day 5			
On Day 3	20 (6.6%)	13 (4.3%)	3 (3.1%)
On Day 4	37 (12.2%)	26 (8.6%)	7 (7.2%)
Missed Day 5 visit/discontinuation	15 (5.0%)	11 (3.7%)	5 (5.2%)
Total missing	72 (23.8%)	50 (16.6%)	15 (15.5%)
Source: Sponsor's electronic SAS data set (Size.xpt) at location of \\cdsesub1\n21727\n_000.			

Results of Table 5 are summarized by the following:

- Among missing data on Day 5, the healing rates prior to Day 5 were 79.2% (57 out of 72), 78.0% (39 out of 50), and 66.7% (10 out of 15) in amlexanox, vehicle and no-treatment group, respectively. Amlexanox patch and vehicle patch are comparable, and higher than the no-treatment group.
- Per clinical comments, patients who had all treated ulcers healed on Days 3 or 4 are unlikely to be "*not healed*" on Day 5.
- The missing data rates due to missing Day 5 visit/discontinuation from the study are comparable between treatments (5.0% vs. 3.7% vs. 5.2% for amlexanox vs. vehicle vs. no-treatment). Following reviewing the data of the primary efficacy endpoint for these patients, they had non-zero total ulcer size in the previous visits. Consequently, efficacy results based on the last observation carried forward (LOCF) approach would be identical to those by imputing them as "not healed" (or failures).

3.1.1.5 Treatment Effect Over Time

To examine the efficacy trend of treatment groups over time, results of the primary efficacy endpoint over time are presented in Table A.3 of the Appendix. Note that the table is intended to observe efficacy trend, otherwise, a multiplicity adjustment would be needed for treatment comparisons at multiple time points. The summary is:

- The response rates increased over time for each of the three treatment groups.
- The response rates of amlexanox patch were better than vehicle and no-treatment arms on Days 3, 4, 5 and 6. However, it was numerically better than no-treatment arm, but numerically worse than vehicle patch on Day 7. The difference between amlexanox and vehicle is not statistically significant (p-value = 0.560). The response rates on Day 7 were 50.8%, 52.8% and 48.5% for amlexanox, vehicle and no-treatment group, respectively.

Discussion:
A request for the explanation on why the efficacy trend of the complete ulcer healing rate reversed on Day 7, with the vehicle patch showing a better outcome than amlexanox, was made by the clinical reviewer on the Division's Filing Review Letter to the sponsor dated 2/20/04. Sponsor's response (dated 3/15/04) stated that the primary reason for the efficacy trend reversion is due to the healing rate pattern in patients with more than one ulcer. The subgroup results on the complete ulcer healing rate over the baseline number of treated ulcers on Day 7 are presented in Table 6.

The sponsor stated (page 2 of Module 5, Vol.5.1 dated 3/15/04) that there was a small imbalance between the amlexanox group and the vehicle group in the number of patients who treated more than one ulcer (i.e., 28% and 23% in the respective group). However, from statistical point of view, the sponsor's argument is not justified for the following reasons:

- For patients with two or three ulcers, amlexanox is numerically worse than not only vehicle, but also the no-treatment group with respect to the complete ulcer healing rate (Table 6). It should be noted that there were about 30% of patients having 2 or 3 treated ulcers in the no-treatment group, as compared to amlexanox group of 28%.
- The three treatment groups are statistically comparable with respect to the number of treated ulcers at baseline (overall p-value = 0.632 based on CMH test in Table A.2 of the Appendix; and 0.208 for the comparison between amlexanox and vehicle in patients who had one vs. more than one treated ulcers).

Table 6: Percentage of Patients with Complete Ulcer Healing on Day 7 by the Number of Treated Ulcers – Study 1U106

ITT Analysis on Day 7	Amlexanox (N = 303)	Vehicle (N = 301)	No-treatment (N = 97)
Overall, n (%)	154 (50.8%)	159 (52.8%)	47 (48.5%)
One treated ulcer	131/219 (59.8%)	133/231 (57.6%)	38/68 (55.9%)
Two treated ulcers	18/58 (31.0%)	18/50 (36.0%)	7/21 (33.3%)
Three treated ulcers	5/26 (19.2%)	8/20 (40.0%)	2/8 (25.0%)
Source: Sponsor's NDA submission (dated 3/15/04, Module 5, Vol.5.1, pages 15-17).			

3.1.2 Supportive Study 9E03

The study drug in trial 9E03 was the early formulation which is different from the final formulation to-be-marketed. As both formulations have the active ingredient of amlexanox 2 mg, study 9E03 is reviewed as supportive.

Study Design

The design of study 9E03 was similar to that of study 1U106 except that only one ulcer was treated per patient. It was designed as multi-investigator (17 U.S. centers and 1 Northern Ireland center), vehicle and no-treatment controlled, investigator-blind and randomized. The study was conducted during June 2000 and December 2000, which was earlier than study 1U106. Three treatments were included, amlexanox patch (early formulation), vehicle patch, and no-treatment. The primary objective was to evaluate the efficacy and safety of amlexanox on the healing rate of recurrent aphthous ulcers as compared to vehicle and no-treatment arms.

A total of 401 patients were randomized in a ratio of 2:2:1 to amlexanox, vehicle and no-treatment groups, respectively. The randomization resulted in 157, 163 and 81 patients in the respective group. Sponsor's randomization list consisted of a total of 100 blocks of size 5 treatment assignments which were generated by a computer algorithm prior to the start of the study. During the course of the trial, 10 (2.5%) patients were randomized out of sequence at study site 133. It is expected that the effect of study site 133 on the efficacy results is not pronounced.

Efficacy Endpoints Specified in the Protocol and Submission

It should be noted that the study protocol was dated 4/24/00 and the study was conducted during June 2000 and December 2000. There were 3 protocol amendments. They are described by the following:

- Amendment #1 (dated 5/17/00): clarification of
  - Inform consent must be signed prior to any study-related procedure.
  - Any change to the protocol would be submitted to the reviewing IRBs.
- Amendment #2 (dated 8/2/00): change of inclusion criterion to include patients with some systemic illness.
- Amendment #3 (dated 8/4/00):
  - Change of the primary efficacy endpoint from the percentage of patients free of pain to the percentage of patients with complete ulcer healing (ulcer size of 0 mm^2) on Day 5.
  - Recalculation of sample size based on the new primary efficacy endpoint.
  - Addition of regression analyses for the primary and the secondary efficacy endpoints to the protocol.

It should be noted that no change on the study size was affected due to the above amendments. Based on the new primary efficacy endpoint, the planned sample size 160, 160, and 80 for amlexanox, vehicle and no-treatment groups provided about 60% power to detect a treatment difference between amlexanox patch and vehicle patch. A logistic regression analysis was added as a secondary analysis for the primary efficacy endpoint at each study day. According to Amendment #3, treatment, center and baseline characteristics would be tested as potential covariates each using a 5% significance level. Sponsor's final Statistical Analysis Plan (SAP,

dated 11/1/00) changed the test to establish non-inferiority of vehicle patch versus no-treatment as follows:

"*To establish non-inferiority of the vehicle disc relative to the no treatment group, 97.5% one-sided confidence interval will be provided for vehicle disc versus no treatment. One-sided tests at the 0.05 significance level will also be performed*".

However, the change did not pre-specify a margin for the non-inferiority assessment. As a result, sponsor's efficacy endpoints specified in the protocol and amendments are:

Primary: percentage of patient with complete ulcer healing on Day 5.
Secondary:

a. Percentage of patients with complete ulcer healing at other study visits.
b. Percentage of patients with complete resolution of pain at each study visit.
c. Time to healing.

Sponsor's safety included the incidence, severity and relationship of adverse events.

Population Analyzed in the Protocols and Submission

The ITT and efficacy evaluable populations were proposed for efficacy analyses. Sponsor's ITT population included all randomized subjects whether or not they ingested one dose of study medication. The efficacy evaluable population was defined as patients who:

- Completed follow-up through healing of the ulcer or through Day 7 if the ulcer did not heal prior to Day 7;
- Did not use analgesic (oral or topical) or any other aphthous ulcer treatments during the course of the study;
- Were compliant with study visit schedule and did not miss more than one visit;
- Filled out the daily oral pain record such that there were not more than 2 consecutive missing pain scores.

Sponsor's safety population included all randomized patients.

Statistical Analysis Plan in the Protocol and Submission

- The CMH test stratifying by center was proposed as the primary analysis method to test the difference among three treatment groups. If the overall treatment effect was significant, pairwise comparisons were made based on 95% confidence interval on the difference of healing rates for two groups. A logistic regression analysis was proposed as the secondary analysis method for healing rate. Treatment, center and baseline characteristics would be tested as potential covariates each using a 5% significance level.
- The percentage of patients with complete resolution of pain was analyzed in the same manner as the primary efficacy endpoint.
- Survival analysis was proposed to analyze median time-to-healing for each pair of treatment groups in the protocol. In addition, results based on Cox proportional hazards approach, which was not pre-specified in the protocol, are also submitted in the NDA.

***Reviewer's Comments on Study 9E03*:**

1. In agreement with the clinical team, the following efficacy endpoints are reviewed to be consistent to those in study 1U106. Results of other endpoints are not reported.

Primary: Percentage of patients with complete ulcer healing on Day 5.
Secondary:
- Percentage of patients with complete resolution of pain on Day 5.
- Time to healing based on the complete ulcer healing.
- Time to healing based on the complete resolution of pain.

2. For the analysis of the primary efficacy endpoint, sponsor's results based on logistic regression in the NDA submission adjusted for age, sex, baseline ulcer size, baseline ulcer number, number of years of ulcers, and abnormal laboratory values at baseline. These covariates were not pre-specified in the protocol. As post-hoc analyses should not be used to establish efficacy, the analysis based on CMH test adjusting for study site is the primary focus in this review. As supportive, analyses based on the logistic regression were performed by the reviewer. The model included only terms of treatment, investigator, and treatment-by-investigator interaction. The interaction was tested at a level of 0.10.

3. As the sponsor did not specify the non-inferiority margin for the comparison between vehicle patch and the no-treatment arm in their protocol, in agreement with the clinical team, the non-inferiority margin of 8%, as in study 1U106, is used. The non-inferiority assessment in the review is based on one-sided 97.5% confidence interval for treatment difference instead of odds ratio in the sponsor's NDA submission. The superiority comparison of amlexanox patch to vehicle patch is tested at a two-sided significance level of 0.05.

4. For the endpoints of time to healing, only results based on survival analysis (i.e., log-rank and Wilcoxon tests) are presented in the review, as Cox proportional hazards approach was not pre-specified in the protocol.

5. As study 9E03 is reviewed as supportive for efficacy claim, there is an issue about common investigators participated in both studies 1U106 and 9E03. This might violate the independence of clinical studies for establishing efficacy. The seven common investigators [redacted] The patient enrollment for these investigators accounted for about 27.4% (192/701) and 49.6% (199/401) of the total enrollment in studies 1U106 and 9E03, respectively.

   A sensitivity analysis is conducted to address this issue in the efficacy result section.

3.1.2.1 Patient Disposition and Baseline Characteristics

The comparability between treatments with respect to patient disposition is presented in Table 7. The patient enrollment by investigator and patient demographics and baseline characteristics are presented in Tables A.4 and A.5 of the Appendix, respectively.

Generally, treatment groups are comparable with respect to the ITT, efficacy-evaluable and safety populations (Table 7). About 96.8%, 96.9% and 95.1% of patients completed the study in amlexanox, vehicle and the no-treatment arms, respectively. No outstanding difference between treatments is noted. For demographics and baseline characteristics, three treatment arms are generally comparable. The study enrolled about 7.6%, 6.7% and 4.9% pediatric patients in amlexanox, vehicle and no-treatment groups, respectively. There is no significant difference among treatment groups in mean age (p-value = 0.595, Table A.5). Most enrolled patients are Caucasian (80.3%, 86.5% and 86.4% in the respective group). There is an imbalance among treatment groups with respect to gender and baseline ulcer size (p-value = 0.05 and 0.088, respectively, in Table A.5 of the Appendix). Vehicle group had a relatively lower female

enrollment rate than other treatment groups (57.1% vs. 66.9% and 71.6%). On the other hand, vehicle group had a larger mean ulcer size at baseline for treated ulcers, a size of 12.4 mm^2 as compared to 10.2 mm^2 and 9.1 mm^2 for amlexanox and no-treatment arms. Subgroup results are examined in the review to investigate the impact of the imbalance of gender and baseline ulcer size to the efficacy results.

Table 7: Patient Disposition – Study 9E03

Subjects	Amlexanox	Vehicle	No-treatment	Overall
Subject Enrolled	157	163	81	401
Completed study	152 (96.8%)	158 (96.9%)	77 (95.1%)	387 (96.5%)
ITT population	157 (100%)	163 (100%)	81 (100%)	401 (100%)
Patients withdrew after randomization	5 (3.2%)	5 (3.1%)	4 (4.9%)	14 (3.5%)
Discontinued, total	5 (3.2%)	5 (3.1%)	4 (4.9%)	14 (3.5%)
Adverse event	2 (1.3%)	1 (0.6%)	0	3 (0.7%)
Patient's request	0	2 (1.2%)	3 (3.7%)	5 (1.2%)
Protocol violation	3 (1.9%)	0	0	3 (0.7%)
Lost to follow-up	0	0	1 (1.2%)	1 (0.2%)
Other reason	0	2 (1.2%)	0	2 (0.5%)
Efficacy evaluable population	145 (92.4%)	155 (95.1%)	76 (93.8%)	376 (93.8%)
Safety population	157 (100%)	163 (100%)	81 (100%)	401 (100%)

Source: Sponsor's NDA submission (Module 5, Vol.1.9, page 43).

3.1.2.2 Primary Efficacy Endpoint

The primary efficacy endpoint is the percentage of patients with complete ulcer healing on Day 5. The efficacy objectives are to establish that (1) amlexanox is superior to vehicle; and (2) vehicle is non-inferior to the no-treatment arm.

In agreement with the clinical team, the non-inferiority margin of 8%, as in study 1U106, is used to establish the non-inferiority assessment between vehicle patch and the no-treatment group. Results are presented in Table 8.

Table 8: Percentage of Patients with Complete Ulcer Healing on Day 5 Study 9E03

Analysis	Amlexanox	Vehicle	No-treatment
ITT	76/157 (48.4%)	58/163 (35.6%)	23/81 (28.4%)
Comparison[1]			
Amlexanox vs. Vehicle	0.026		
Vehicle vs. No-treatment	–5.6%		
Efficacy-Evaluable	72/145 (49.7%)	57/155 (36.8%)	22/76 (28.9%)
Comparison[1]			
Amlexanox vs. Vehicle	0.042		
Vehicle vs. No-treatment	–4.9%		

Source: Sponsor's NDA submission (Module 5, Vol.1.9, pages 116-117).
[1] The comparison (p-value) between amlexanox and vehicle was based on CMH test adjusting for investigator. The listing for the comparison between vehicle and no-treatment was the exact lower limit of one-sided 97.5% confidence interval of the treatment difference (i.e., Vehicle – No-treatment) using StatXact Version 5.

The summary of Table 8 is:

- Point estimates based on the ITT and efficacy evaluable populations are generally consistent.
- Amlexanox is statistically superior to vehicle based on both the ITT and efficacy-evaluable analyses (p-value = 0.026 and 0.042, respectively). The ITT healing rates are 48.4% vs. 35.6% for amlexanox vs. vehicle.
- The non-inferiority assessment of vehicle patch vs. no-treatment is established because the lower limits of the one-sided 97.5% confidence interval based on the ITT and efficacy evaluable populations (i.e., –5.6% and –4.9%) are greater than –8%.
- Note that the healing rates for each treatment in study 9E03 are considerably higher than those in study 1U106 (i.e., ITT response rates of 48.4%, 35.6%, and 28.4% in study 9E03 vs. 30.4%, 21.9% and 21.6% in study 1U106). More discussion on this point is included in Section 3.1.2.7.

As supportive, analyses based on the logistic regression were performed. The logistic regression model included treatment, investigator and treatment-by-investigator interaction. The interaction term was tested at a significance level of 0.10. The ITT analysis shows that amlexanox is superior to vehicle with p-value of 0.023. To ensure the efficacy benefit of amlexanox, the comparison between amlexanox and no-treatment is performed. Amlexanox is superior to the no-treatment arm (p-value = 0.005 and 0.004 based on CMH test adjusted for center and logistic regression method, respectively).

3.1.2.3 Secondary Efficacy Endpoints

In agreement with the clinical team, the following secondary efficacy endpoints are reviewed:

a. Time to complete ulcer healing
b. Percentage of patients with complete resolution of pain on Day 5
c. Time to complete resolution of pain

Results are presented in Tables 9.a-9.b. The summary is:

- Results based on the ITT and efficacy-evaluable populations are generally consistent.
- Comparison between amlexanox and vehicle:
  - The superiority of amlexanox to vehicle is ***not*** established with respect to the percentage of patients with complete resolution of pain on Day 5 (p-value = 0.409 and 0.512 for the ITT and efficacy-evaluable analyses, Table 9.a). This is confirmed by the analyses of time to complete resolution of pain based on log-rank and Wilcoxon tests (p-value $\geq$ 0.208 for the ITT analysis and p-value $\geq$ 0.280 for the efficacy-evaluable analysis, Table 9.b).
  - Amlexanox is superior to vehicle in terms of the time to complete ulcer healing regardless of log-rank test or Wilcoxon test (p-value $\leq$ 0.034 for the ITT analysis and $\leq$ 0.048 for the efficacy-evaluable analysis, Table 9.b).
- Amlexanox is superior to the no-treatment arm with respect to each of the secondary efficacy endpoints (Tables 9.a – 9.b) regardless of populations analyzed.

Table 9.a: Percentage of Patients with Complete Resolution of Pain on Day 5 – Study 9E03

Analysis	Amlexanox	Vehicle	No-treatment
ITT	94/157 (59.9%)	90/163 (55.2%)	32/81 (39.5%)
Comparison (p-value)[1]			
Amlexanox vs. Vehicle	0.409		
Amlexanox vs. No-treatment	0.002		
Efficacy Evaluable	88/145 (60.7%)	88 /155 (56.8%)	31/76 (40.8%)
Comparison (p-value)[1]			
Amlexanox vs. Vehicle	0.512		
Amlexanox vs. No-treatment	0.003		

Source: Sponsor's NDA submission (Module 5, Vol.1.9, pages138-139).
[1] The p-value for the comparison of amlexanox and vehicle was based on two-sided CMH test adjusting for investigator; while the p-value for the comparison of vehicle and no-treatment was based on one-sided CMH test adjusting for investigator.

Table 9.b: Time to Healing Based on Ulcer Size and Complete Resolution of Pain – Study 9E03

Treatment/comparison	Median time to healing (in days)	Log-Rank test (p-value)	Wilcoxon test (p-value)
Time to complete ulcer healing			
ITT			
Amlexanox patch	5.0		
Vehicle patch	5.0		
No-treatment	6.0		
Comparison			
Amlexanox vs. Vehicle		0.034	0.019
Amlexanox vs. No-treatment		0.003	0.004
Efficacy Evaluable			
Amlexanox patch	5.0		
Vehicle patch	5.0		
No-treatment	6.0		
Comparison			
Amlexanox vs. Vehicle		0.048	0.026
Amlexanox vs. No-treatment		0.003	0.004
Time to complete resolution of pain score			
ITT			
Amlexanox patch	4.0		
Vehicle patch	4.0		
No-treatment	5.5		
Comparison			
Amlexanox vs. Vehicle		0.283	0.208
Amlexanox vs. No-treatment		0.002	< 0.001
Efficacy Evaluable			
Amlexanox patch	4.0		
Vehicle patch	4.0		
No-treatment	5.0		
Comparison			
Amlexanox vs. Vehicle		0.313	0.280
Amlexanox vs. No-treatment		0.002	< 0.001

Source: Sponsor's NDA submission (Module 5, Vol.1.9, pages 123-125, 147-149).

3.1.2.4 Effect of Missing Data Handling

Though no method of handling missing data was pre-specified in the protocol, the sponsor imputed missing on Day 5 as "not healed" in the NDA submission. To examine the robustness of the missing data handling on efficacy results, missing data pattern is examined. A total of 39 (24.8%), 30 (18.4%) and 16 (19.8%) patients had missing measurements on Day 5 in amlexanox, vehicle and no-treatment arm, respectively. The reasons for missing measurements included

healed prior to Day 5 and left the study, missed Day 5 visit, and discontinued from the study. The detail is presented in Table 10. Results are summarized by the following:

- The missing data rate due to complete ulcer healing prior to Day 5 were 87.2% (34 out of 39), 83.3% (25 out of 30), and 81.3% (13 out of 16) in amlexanox, vehicle and no-treatment group, respectively. Amlexanox had a numerically higher ulcer healing rate prior to Day 5 than other groups.
- Per clinical comments, patients who had all treated ulcers healed on Days 3 or 4 are unlikely to be "*not healed*" on Day 5.
- The missing data rates due to missing Day 5 visit/discontinuation from the study are small and comparable between treatments (3.2% vs. 3.1% vs. 3.7% for amlexanox vs. vehicle vs. no-treatment). Data on the total ulcer size for these patients were reviewed. All the patients had non-zero total ulcer size in the previous visits. Consequently, efficacy results based on the LOCF approach would be identical to those by imputing them as "not healed" (or failures).

Table 10: Missing Data Pattern on Day 5 – Study 9E03

Reasons for Missing Data on Day 5	Amlexanox (n = 157)	Vehicle (n = 163)	No-treatment (n = 81)
All treated ulcers healed prior to Day 5			
On Day 3	14 (8.9%)	9 (5.5%)	4 (4.9%)
On Day 4	20 (12.7%)	16 (9.8%)	9 (11.1%)
Missed Day 5 visit/discontinuation	5 (3.2%)	5 (3.1%)	3 (3.7%)
Total missing	39 (24.8%)	30 (18.4%)	16 (19.8%)
Source: Sponsor's electronic SAS data sets.			

3.1.2.5 Treatment Effect over Time

Similar to study 1U106, results of the primary efficacy endpoint over time are presented in Table A.6 of the Appendix for study 9E03. The table is intended to explore efficacy trend, otherwise, a multiplicity adjustment would be needed for treatment comparisons at multiple time points. The summary is:

- The response rates increased over time for each of the three treatment groups.
- The response rates of amlexanox were better than vehicle and no-treatment arm on each assessment day. Vehicle patch is better than no-treatment arm on all assessment days except on Day 4 (15.3% vs. 16.0%). The superiority of amlexanox to vehicle is established statistically only on Day 5.

3.1.2.6 Sensitivity Analyses

Even though study 9E03 is reviewed as supportive, it should be noted that 7 investigators participated in both studies 1U106 and 9E03. This might violate the independence of clinical studies for establishing efficacy. The seven common investigators [

] The patient enrollment for the 7 investigators accounted for 27.4% (192/701) and 49.6% (199/401) of the study enrollment in 1U106 and 9E03, respectively. The potential statistical issues are:

- Independence of the two studies (7 common investigators in two studies).
- Among 192 patients in study 1U106, number of patients also participated in study 9E03.

The following addresses these issues.

1. Independence of the Studies

Efficacy results are presented in Table 11 for the 7 investigational sites vs. the remaining sites for studies 1U106 and 9E03. Results by individual site are presented in Tables A.7-A.8 of the Appendix for both studies.

Table 11: Percentage of Patients with Complete Ulcer Healing on Day 5 (ITT) Studies 1U106 and 9E03

Study (duration)	Study site	Amlexanox (A)	Vehicle (V)	No-treatment (N)	Comparison[1]	p-value or LL
9E03 (6/00 – 12/00)	Overall	76/157 (48.4%)	58/163 (35.6%)	23/81 (28.4%)	A vs. V A vs. N LL for V vs. N[2]	0.026 0.005 –5.6%
	The 7 site	41/78 (52.6%)	31/81 (38.3%)	12/40 (30.0%)	A vs. V A vs. N LL for V vs. N[2]	0.072 0.024 –10.4%
	Remaining sites	35/79 (44.3%)	27/82 (32.9%)	11/41 (26.8%)	A vs. V A vs. N LL for V vs. N[2]	0.179 0.082 –12.0%
1U106 (6/02 – 3/03)	Overall	92/303 (30.4%)	66/301 (21.9%)	21/97 (21.6%)	A vs. V A vs. N LL for V vs. N[2]	0.015 0.093 –9.2%
	The 7 sites	27/84 (32.1%)	18/82 (22.0%)	10/26 (38.5%)	A vs. V A vs. N LL for V vs. N[2]	0.148 0.540 –38.2%
	Remaining sites	65/219 (29.7%)	48/219 (21.9%)	11/71 (15.5%)	A vs. V A vs. N LL for V vs. N[2]	0.037 0.016 –4.8%

Source: Reviewer's analysis based on the sponsor's electronic SAS data sets.
[1] Comparisons of A vs. V and A vs. N each is based on CMH test adjusting for study site; the comparison of V vs. N is based on the lower limit of one-sided 97.5% confidence interval for (vehicle – no-treatment).
[2] LL for V vs. N is the exact lower limit of one-sided 97.5% confidence interval computed using StatXact version 5.

The summary is:

- For each study, the ulcer healing rates in the 7 sites are larger than those of the remaining sites regardless of treatment groups.
- As study 9E03 was conducted earlier than study 1U106 (June 2000 – December 2000 vs. June 2002 – March 2003), analyses with and without the 7 sites were compared for study 1U106. The summary is:
  - The ulcer healing rates with and without the 7 sites are generally comparable in amlexanox and vehicle arms. On the other hand, the 7 sites had an exceptionally high ulcer healing rate in the no-treatment arm as compared to the remaining sites (38.5% vs. 15.5%, Table 11).
  - For independence of the two studies, results of study 1U106 excluding the 7 sites show
    a. The superiority of amlexanox to vehicle (p-value = 0.037), and superiority of amlexanox to no-treatment (p-value = 0.016) and
    b. Vehicle patch is non-inferior to the no-treatment arm because the lower limit of the one-sided 97.5% confidence interval for (Vehicle – No-treatment) is –4.8%, which is greater than the non-inferiority margin of –8%.

2. Patients Participation in the Two Studies

Another issue is the number of patients participated in both studies. A request concerning this point was sent to the sponsor. Sponsor's responses (dated 3/24/04) included documents of patient initials at the seven investigational sites for the two studies. The submission indicated that the maximum number of patients participated in the two trials is 4 (accounted for 0.6% and 1% of patient enrollment in studies 1U106 and 9E03, respectively). The patient IDs are 104, 106, 135 and 693 for study 1U106 which are corresponding to patient IDs of 272, 037, 433 and 177 for study 9E03. This is not expected to affect the efficacy conclusions.

3. Other Issues

Another note is that 10 patients at study site 133 were randomized out of sequence in study 9E03. This would not affect the efficacy conclusions for the following reasons:

- Ten patients accounted for only about 2.5% of the study enrollment.
- The complete ulcer healing rates at study site 133 were 2/4 (50%), 3/4 (75%) and 2/2 (100%) for amlexanox patch, vehicle patch and no-treatment arm, respectively (Table A.8 of the Appendix). Vehicle and the no-treatment groups did exceptionally well than amlexanox. However, it is difficult to make definite conclusion because of small sample sizes. Efficacy results by excluding study site 133 would be in favor of amlexanox. The efficacy conclusions remain the same.

3.1.2.7 Other Discussions

It should be noted that the overall complete ulcer healing rates of study 1U106 are considerably lower than those of study 9E03 regardless of treatment groups. One possible explanation is that study 1U106 allowed treating up to 3 ulcers per patient. To investigate this issue, results of the complete ulcer healing rate by the number of treated ulcers are presented in Table A.9 of the Appendix.

For study 1U106, the complete ulcer healing rates on Day 5 for patients with only one treated ulcers were 36.5%, 25.5% and 27.9% in amlexanox, vehicle and no-treatment. They are lower than those in study 9E03 (48.4%, 35.6% and 28.4% in the respective group), in particular, the healing rates for amlexanox and vehicle groups. Patients with 3 treated ulcers accounted for only about 8% of the study enrollment. Amlexanox is numerically worse than vehicle and the no-treatment groups with respect to the complete ulcer healing rate on Day 5 for these patients. The complete ulcer healing rates are 7.7% vs. 15.0% vs. 12.5% for amlexanox vs. vehicle vs. no-treatment. Consequently, there may be insufficient data to evaluate the efficacy claim for the treatment of 3 ulcers.

3.2 Evaluation of Safety

Safety assessment based on the incidence rates of adverse event (AE), serious adverse events and withdrawals due to adverse events is summarized in Tables 12-13 for studies 1U106 and 9E03, respectively. The safety profile of amlexanox is generally comparable to vehicle:

➢ Study 1U106 (Table 12) –

- The overall adverse event incidence rates are comparable between treatments (19.8% vs. 23.6% vs. 15.5% for amlexanox vs. vehicle vs. no-treatment).

- About 15.2%, 16.9% and 1.0% of patients had adverse events potentially related to treatment. Note that one patient in the no-treatment group had an adverse event potentially related to study medication (Ear/labyrinth disorders). This might be due to an error in reporting.
- Most treatment-related adverse events were classified as application site reaction. The incidence rates were 12.5% and 14.0% for amlexanox and vehicle groups, respectively. The most frequent treatment-related application site adverse event was pain with 8.6% and 7.6% of patients in the respective group.

➢ Study 9E03 (Table 13) –

- The overall adverse event incidence rates are comparable between amlexanox and vehicle treatments (29.3% vs. 26.4%).
- About 9.6% and 7.4% of patients had treatment-related application site adverse events in amlexanox and vehicle treatments, respectively. The most frequent events were burning and pain with 4.5% and 3.8% in amlexanox arm and 2.5% and 3.7% in vehicle group.
- For events other than the application sites, the most frequent treatment-related event was gastrointestinal disorder with about 4.5% vs. 6.1% for amlexanox patch vs. vehicle patch.

Table 12: Number (%) of Patients Had Adverse Events – Study 1U106

Event	Amlexanox (n = 303)	Vehicle (n = 301)	No-treatment (n = 97)
All Events			
All Adverse Events	60 (19.8%)	71 (23.6%)	15 (15.5%)
Application Site Reactions # Patients with AE	38 (12.5%)	44 (14.6%)	0
AE other than application sites # Patients with AE	26 (8.6%)	39 (13.0%)	15 (15.5%)
# patients withdrew due to AE	0	4 (1.3%)	0
# patients had serious AE	0	0	0
Events Potentially Related to Treatment			
All Adverse Events	46 (15.2%)	51 (16.9%)	1 (1.0%)
Application Site Reactions # Patients with AE	38 (12.5%)	42 (14.0%)	0
Pain	26 (8.6%)	23 (7.6%)	0
Burning	8 (2.6%)	9 (3.0%)	0
Irritation	5 (1.7%)	6 (2.0%)	0
Paresthesia	3 (1.0%)	4 (1.3%)	0
Reaction NOS	3 (1.0%)	0	0
Bleeding	1 (0.3%)	0	0
Oedema	1 (0.3%)	1 (0.3%)	0
Ulcer	1 (0.3%)	1 (0.3%)	0
Anaesthesia	0	1 (0.3%)	0
AE other than application sites # Patients with AE	10 (3.3%)	14 (4.7%)	1 (1.0%)
Gastrointestinal disorders	6 (2.0%)	10 (3.3%)	0
Nervous system disorders	2 (0.7%)	4 (1.3%)	0
Eye disorders	1 (0.3%)	0	0
General disorders	1 (0.3%)	1 (0.3%)	0
Musculoskeletal/bone disorders	1 (0.3%)	0	0
Skin/subcutaneous tissue	1 (0.3%)	1 (0.3%)	0
Ear/labyrinth disorders	0	0	1 (1.0%)

Source: Sponsor's NDA submission (Module 5, Vol.1.3, pages 74-78, 181-187).

Table 13: Number (%) of Patients Had Adverse Events – Study 9E03

Event	Amlexanox (n = 157)	Vehicle (n = 163)	No-treatment (n = 81)
All Events			
All Adverse Events	46 (29.3%)	43 (26.4%)	5 (6.2%)
Application Site Reactions # Patients with AE	15 (9.6%)	12 (7.4%)	0
AE other than application sites # Patients with AE	32 (20.4%)	37 (22.7%)	5 (6.2%)
# Patients withdrew due to AE	2 (1.3%)	1 (0.6%)	0
# patients with serious AE	0	0	0
Events Potentially Related to Treatment			
Application Site Reactions			
# Patients with AE	15 (9.6%)	12 (7.4%)	0
Burning	7 (4.5%)	4 (2.5%)	0
Pain	6 (3.8%)	6 (3.7%)	0
Anaesthesia	1 (0.6%)	1 (0.6%)	0
Bleeding	1 (0.6%)	0	0
Irritation	1 (0.6%)	0	0
Dryness	0	1 (0.6%)	0
Oedema	0	1 (0.6%)	0
Paresthesia	0	1 (0.6%)	0
Reaction NOS	0	1 (0.6%)	0
AE other than application sites			
# Patients with AE	10 (6.4%)	13 (8.0%)	0
Gastrointestinal disorders	7 (4.5%)	10 (6.1%)	0
Nervous system disorders	3 (1.9%)	2 (1.2%)	0
Respiratory/thoracic/mediastinal	0	1 (0.6%)	0

Source: Sponsor's NDA submission (Module 5, Vol.1.9, pages 71-75, 153-157).

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup results on the percentage of patients with complete ulcer healing on Day 5 over gender, race, age (pediatric, adult and geriatric), baseline number of treated ulcers, baseline ulcer size, and baseline pain score are examined. The results are presented in Tables A.10 – A.11 of the Appendix for studies 1U106 and 9E03, respectively. It should be noted that subgroup results are intended to explore efficacy trend over subgroups. The studies were not designed to test efficacy within subgroups.

4.1 Gender, Race and Age

Generally, the response rates of amlexanox patch are larger than vehicle patch and no-treatment group regardless of gender for each of studies 1U106 and 9E03. Note that the ulcer healing rates for female patients are numerically higher than those of male group for each treatment arm in each study. A logistic regression analysis with terms of treatment group, gender, and treatment-by-gender interaction was performed. There is a significant gender effect as p-value = 0.093 and 0.037 for studies 1U106 and 9E03, respectively. As the study duration was 7-day, no outstanding compliance problems are noted. The complete ulcer healing rate over gender is further examined in terms of the baseline ulcer size and the number of treated ulcer. The results are presented in Tables A.12-A.14 of the Appendix. The summary is:

- Baseline ulcer size (Tables A.12-13):
  - Overall, the male patients had numerically higher mean ulcer size at baseline than female patients for each treatment group in each study except the vehicle group in study 1U106.

- Generally, the mean ulcer size is smaller for patients who had complete ulcer healing on Day 5 regardless of gender. Note that the mean ulcer size for female subjects who had complete ulcer healing on Day 5 are numerically larger than that of male patients in amlexanox and vehicle groups for study 1U106; while in amlexanox and no-treatment groups for study 9E03. No trend of smaller ulcer size for female subjects is noted from both studies.

- Number of treated ulcer (Table A.14):
  As study 9E03 treated one ulcer per patient, results by the number of treated ulcer only apply to study 1U106. Patients with one treated ulcer had higher chance of success regardless of gender and treatment groups. Female patients generally had numerically higher complete ulcer healing rate than male patients for 1 or 2 treated ulcers at baseline. The difference is small in amlexanox and no-treatment groups for 1 treated ulcer (37.1% vs. 35.4% in amlexanox; while 28.3% vs. 27.3% in the no-treatment group). No other outstanding issue is noted.

More than 80% of subjects are Caucasian, the ulcer healing rates for Caucasian patients are similar to those based on the whole ITT population. The healing rates of Caucasian and Hispanic are larger in amlexanox treatment as compared to other treatments. There may be a large variation of response rates for Asian and Other race groups; however, it is difficult to make a definite conclusion about treatment comparisons, as the sample sizes are small.

Age was divided into three groups, pediatric, adult and geriatric. About 85% and 91% of patients are adults in studies 1U106 and 9E03, respectively. The efficacy results of adult group are similar to those based on the whole ITT population. For pediatric patients in study 1U106, amlexanox is better than vehicle, but worse than the no-treatment. The healing rate in amlexanox is similar to the overall rate (29.7% vs. 30.4%). However, the pediatric response rates of vehicle and the no-treatment groups are higher than the overall rates (26.5% vs. 21.9% for vehicle, and 33.3% vs. 21.6% for the no-treatment). For the pediatric patients in study 9E03, the healing rate in amlexanox group is numerically worse than that of other treatments (25.0% vs. 27.3% vs. 75.0%). The ulcer healing rates of pediatric subjects were considerably lower in amlexanox and vehicle groups as compared to the no-treatment group. However, it is difficult to make definite conclusions, as pediatric patients accounted for only about 6.7% of the total enrollment in study 9E03.

4.2 Other Special/Subgroup Populations

Subgroup efficacy results by baseline number of treated ulcers, baseline ulcer size, and baseline pain score are presented. The complete ulcer healing rate generally decreases as the baseline number of treated ulcers, ulcer size and pain score increases in study 1U106. For patients treated with 3 ulcers, it should be noted that amlexanox is numerically worse than vehicle and the no-treatment groups. The ulcer healing rates are 7.7% vs. 15.0% vs. 12.5% for amlexanox vs. vehicle vs. no-treatment. This is in contrast to patients treated with one or two ulcers, where amlexanox is numerically better than the other two groups. As patients with 3 treated ulcers accounted for only about 8% of the study enrollment, there may be insufficient data to evaluate the labeling claim for treatment of 3 ulcers.

For study 9E03, the ulcer healing rate decreases as baseline ulcer size increases in amlexanox and vehicle treatments. The healing rates in amlexanox and vehicle groups are relatively higher with baseline ulcer size of 0 – 20 mm^2 as compared to ulcer size of > 20 mm^2. The response rates are similar between baseline pain score categories in amlexanox and vehicle groups. No other outstanding difference is noted within subgroups.

5 SUMMARY AND CONCLUSIONS

The sponsor submitted results of studies 1U106 and 9E03 for the efficacy claims of OraDisc™, where study 1U106 is the pivotal trial. It should be noted that study 1U106 was conducted based on the final formulation to-be-marketed, and study 9E03 was based on the early formulation. As both formulations have the active ingredient of amlexanox 2 mg, study 9E03 is reviewed as supportive.

5.1 Statistical Issues and Collective Evidence

Even though the Division's recommendation on a "win" for a clinical trial (EOP-2 Meeting dated 8/20/01) were

- Active should be superior to vehicle, and
- Vehicle should be non-inferior to no-treatment

the comparison between amlexanox and no-treatment in study 1U106 is non-significant with respect to the primary efficacy endpoint (p-value = 0.093 and 0.088 based on CMH test adjusted for center and logistic regression method on the ITT population, respectively). This comparison was examined to ensure the efficacy benefit of amlexanox following the fact that the overall non-inferiority of vehicle to no-treatment was not established with respect to the pre-specified margin of 8%, however, the limit was close to the margin. The non-significant results between amlexanox and no-treatment could be attributed to the following factors:

1. The treatment allocation ratio for amlexanox vs. no-treatment was 3:1. The superiority of amlexanox to no-treatment is not established due to a smaller sample size for the no-treatment arm even though the ulcer healing rate for the no-treatment group is similar to that of vehicle patch (21.6% vs. 21.9%).
2. Even though no sample size calculation was considered for the comparison of amlexanox vs. no-treatment at the design stage, the planned sample size along with the assumptions in the sample size calculations would warrant at least an 80% power to demonstrate the superiority of amlexanox over no-treatment. However, the actual response rates in study 1U106 are lower than those of the assumptions. The treatment difference (δ) is 20% based on the assumptions, as compared to 8.7% from the results in study 1U106.

For study 9E03 to be supportive, one statistical issue is that seven investigators participated in both studies 1U106 and 9E03. This might violate the independence of clinical studies for establishing efficacy. The seven common investigators [

] The patient enrollment for these investigators accounted for 27.4% (192/701) and 49.6% (199/401) of the total enrollment in studies 1U106 and 9E03, respectively.

A sensitivity analysis was conducted to examine the impact of the seven common investigators on the efficacy results. Results are presented in the section of conclusion and recommendations.

5.2 Conclusions and Recommendations

The sponsor in this submission presented results of pivotal study 1U106 and supportive study 9E03 in support of the efficacy and safety claim of OraDisc™ (amlexanox patch 2 mg) for the treatment of [redacted] aphthous ulcers. The dosing of OraDisc™ is one patch per ulcer four times daily (after each meal and before bedtime) for up to 7 days or until all ulcers treated have healed, whichever occurs first. The primary efficacy endpoint is the percentage of patients with complete healing of all treated ulcers on Day 5.

Efficacy results based on the ITT population with imputing missing data as "not healed" are presented in Table S.1 for studies 1U106 and 9E03. As up to 3 ulcers per patient were treated in study 1U106 as compared to only one treated ulcer per patient in study 9E03, efficacy results of the complete ulcer healing for study 9E03 and subgroup results over the number of treated ulcers at baseline for study 1U106 are presented in Table S.2.

The following summarizes the results.

Efficacy:

Primary efficacy endpoint –

- Overall, amlexanox is superior to vehicle in study 1U106 (p-value = 0.015, Table S.1). This finding is further supported based on the results in study 9E03 (p-value = 0.026, Table S.1). The overall ulcer healing rates are 30.4% vs. 21.9% for amlexanox vs. vehicle in study 1U106; and 48.4% vs. 35.6% in study 9E03.
- The non-inferiority evaluation of vehicle patch to the no-treatment arm is not established for study 1U106. The lower limit of the one-sided 97.5% confidence interval –9.2% is outside the pre-specified non-inferiority margin of –8%. On the other hand, the non-inferiority of vehicle patch to the no-treatment arm is established in study 9E03 (Table S.1).
- To ensure efficacy benefit of amlexanox, the comparison between amlexanox and the no-treatment arm is examined. The overall superiority of amlexanox to no-treatment is not established for study 1U106 (p-value = 0.093, Table S.1). However, the superiority of amlexanox to no-treatment is established for study 9E03 (p-value = 0.005, Table S.1).
- For 3 treated ulcers, amlexanox was numerically worse than vehicle and no-treatment groups in study 1U106 (Table S.2) with respect to the primary efficacy endpoint. The ulcer healing rates were 7.7% vs. 15.0% vs. 12.5% for amlexanox vs. vehicle vs. no-treatment. As this category of patients accounted for about 8% of the study enrollment, there may be insufficient data to evaluate the labeling claim for treatment of 3 ulcers.
- Female patients did better than male patients with respect to the complete ulcer healing.

Secondary efficacy endpoints –

- In contrast to results of the primary efficacy endpoint, results from studies 1U106 and 9E03 did ***not*** show the superiority of amlexanox to vehicle in pain resolution, measured in terms of the percentage of patients with complete resolution of pain on Day 5, and time to complete

resolution of pain (Table S.1). The superiority of amlexanox to no-treatment is established for complete pain resolution in both trials (Table S.1).

Others –

- There were seven common investigators participated in the two studies. Study 1U106 was conducted later than study 9E03. For the independence of the two studies, results of the primary efficacy endpoint excluding the seven sites for study 1U106 show that amlexanox is superior to vehicle (p-value = 0.037), and to no-treatment arm (p-value = 0.016); and amlexanox is non-inferior to vehicle (limit is –4.8% > –8%, Table S1).
- Vehicle patch had a numerically better (but not statistically) outcome than amlexanox in the ulcer healing rate on Day 7 for study 1U106. The ulcer healing rates on Day 7 were 50.8% vs. 52.8% for amlexanox vs. vehicle.

Table S.1: Efficacy Results for Studies 1U106 and 9E03

Study (duration)	Amlexanox (A)	Vehicle (V)	No-treatment (N)	Comparison	p-value or LL
Primary: percentage of patients with complete healing of all treated ulcers on Day 5					
1U106 – Overall (6/02 – 3/03)	92/303 (30.4%)	66/301 (21.9%)	21/97 (21.6%)	A vs. V[1] A vs. N[1] LL for V vs. N[2]	0.015 0.093 –9.2%
The 7 Sites	27/84 (32.1%)	18/82 (22.0%)	10/26 (38.5%)	A vs. V[1] A vs. N[1] LL for V vs. N[2]	0.148 0.540 –38.2%
Remaining Sites	65/219 (29.7%)	48/219 (21.9%)	11/71 (15.5%)	A vs. V[1] A vs. N[1] LL for V vs. N[2]	0.037 0.016 –4.8%
9E03 (6/00 – 12/00)	76/157 (48.4%)	58/163 (35.6%)	23/81 (28.4%)	A vs. V[1] A vs. N[1] LL for V vs. N[2]	0.026 0.005 –5.6%
Secondary: Percentage of patients with complete resolution of pain on Day 5					
1U106	134/303 (44.2%)	132/301 (43.9%)	30/97 (30.9%)	A vs. V[1] A vs. N[1]	0.988 0.018
9E03	94/157 (59.9%)	90/163 (55.2%)	32/81 (39.5%)	A vs. V[1] A vs. N[1]	0.409 0.002
Secondary: time (in days) to complete resolution of pain					
1U106	5.0	5.0	6.0	A vs. V[3] A vs. N[3]	0.704 0.034
9E03	4.0	4.0	5.5	A vs. V[3] A vs. N[3]	0.283 0.002

[1] Comparisons of A vs. V (Amlexanox vs. vehicle) and A vs. N (Amlexanox vs. no-treatment) are based on CMH test adjusting for study site.
[2] Comparison of V vs. N (vehicle vs. no-treatment) is based on the lower limit of one-sided 97.5% confidence interval for (Vehicle – No-treatment). LL represents the exact lower limit of one-sided 97.5% confidence interval computed using StatXact version 5.
[3] Comparisons are based on log-rank test.

Table S.2: Percentage of Patients with Complete Ulcer Healing on Day 5 By the Number of Treated Ulcer

ITT Analysis	Amlexanox	Vehicle	No-treatment
Study 1U106			
Overall, n (%)	92/303 (30.4%)	66/301 (21.9%)	21/97 (21.6%)
One treated ulcer	80/219 (36.5%)	59/231 (25.5%)	19/68 (27.9%)
Two treated ulcers	10/58 (17.2%)	4/50 (8.0%)	1/21 (4.8%)
Three treated ulcers	2/26 (7.7%)	3/20 (15.0%)	1/8 (12.5%)
Study 9E03			
Overall, n(%)	76/157 (48.4%)	58/163 (35.6%)	23/81 (28.4%)

Safety:

The safety profile of amlexanox patch is generally comparable to vehicle patch in terms of the incidence of adverse event.

- About 12.5% vs. 14.0% of patients in amlexanox vs. vehicle groups experienced treatment-related application site adverse events in study 1U106; while about 9.6% vs. 7.4% of patients in study 9E03.
- The most frequent treatment-related application site adverse event was pain with 8.6% vs. 7.6% of patients in amlexanox vs. vehicle groups for study 1U106. The most frequent treatment-related application site events in study 9E03 were burning and pain with 4.5% and 3.8% in amlexanox arm; and 2.5% and 3.7% in vehicle group.

Note that one patient in the no-treatment group had an adverse event potentially related to the study medication (Ear/Labyrinth disorders) in study 1U106. This might be attributed to an error in reporting.

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APPENDICES

Additional Tables

Table A.1: Patient Enrollment by Investigator – Study 1U106

Investigator ID (Last name)	# patients randomized	Amlexanox	Vehicle	No-treatment
125	11	4	6	1
126	31	14	13	4
127	33	15	14	4
129	27	12	11	4
131	28	12	12	4
132	13	6	5	2
135	49	21	21	7
159	46	19	20	7
160	34	15	14	5
161	44	19	19	6
162	58	24	25	9
163	1	0	1	0
166	6	2	3	1
168	12	6	5	1
169	23	10	10	3
170	32	14	14	4
171	6	3	3	0
172	15	6	7	2
173	27	12	11	4
174	49	21	21	7
175	49	21	21	7
177	12	6	4	2
178	21	9	9	3
180	51	22	22	7
181	4	1	2	1
182	1	0	1	0
183	18	9	7	2
Total	701	303	301	97

Source: Sponsor's electronic SAS data sets at location of \\cdsesub1\n21727\n_000.

Table A.2: Demographic and Baseline Characteristics (ITT) – Study 1U106

Variable	Amlexanox (n = 303)	Vehicle (n = 301)	No-treatment (n = 97)	p-value
Gender				
Female	196 (64.7%)	202 (67.1%)	60 (61.9%)	0.61
Male	107 (35.3%)	99 (32.9%)	37 (38.1%)	
Age				
Mean (s.d.)	29.7 (12.2)	28.9 (12.4)	29.7 (12.4)	0.66
median	26	26	26	
Min – max	12 – 75	12 – 73	12 – 68	
Distribution				
≥ 12 and < 15	15 (5%)	27 (9%)	7 (7%)	
≥ 15 and < 18	22 (7%)	22 (7.3%)	5 (5%)	
≥ 18 and < 65	263 (87%)	248 (82%)	84 (86.6%)	
≥ 65	3 (1%)	4 (1%)	1 (1%)	
Race				
Caucasian	265 (87.5%)	259 (86.0%)	77 (79.4%)	0.60
Hispanic	21 (6.9%)	22 (7.3%)	11 (11.3%)	
Black	6 (2.0%)	7 (2.3%)	2 (2.1%)	
Asian	5 (1.7%)	7 (2.3%)	2 (2.1%)	
Other	6 (2.0%)	6 (2.0%)	5 (5.2%)	
Weight (kg)				
Mean (s.d.)	70.3 (17.2)	72.0 (17.9)	69.8 (15.7)	0.40
Median	66	70	68	
Min – max	42 – 127	29 – 152	40 – 127	
Height (cm)				
Mean (s.d.)	168.1 (10.2)	168.1 (11.0)	168.5 (11.7)	0.96
Median	168	167	168	
Min – max	146 – 203	134 – 202	135 – 192	
Ulcer size (mm^2)				
Mean (s.d.)	14.97 (15.72)	14.67 (17.16)	14.82 (20.82)	0.978
Median	10.00	9.00	9.00	
Min – max	0.25 – 90.0	0.09 – 150.0	0.01 – 135.0	
Number of treated ulcers				
1	219 (72.3%)	231 (76.7%)	68 (70.1%)	0.632
2	58 (19.1%)	50 (16.6%)	21 (21.6%)	
3	26 (8.6%)	20 (6.6%)	8 (8.2%)	

Source: Sponsor's NDA submission (Module 5, Vol.1.3, pages 54 – 56, and page 128) and sponsor's electronic SAS data set (Size.xpt) at location of \\cdsesub1\n21727\n_000.

Table A.3: Number (%) of Patients with Complete Ulcer Healing Over Time (ITT) – Study 1U106

Time	Amlexanox (n = 303)	Vehicle (n = 301)	No-treatment (n = 97)
Day 3	20 (6.6%)	13 (4.3%)	3 (3.1%)
Comparison[1]			
Amlexanox vs. Vehicle	0.192		
Amlexanox vs. No-treatment	0.179		
Vehicle vs. No-treatment	–2.91%		
Day 4	57 (18.8%)	40 (13.3%)	10 (10.3%)
Comparison[1]			
Amlexanox vs. Vehicle	0.055		
Amlexanox vs. No-treatment	0.050		
Vehicle vs. No-treatment	–4.18%		
Day 5	92 (30.4%)	66 (21.9%)	21 (21.6%)
Comparison[1]			
Amlexanox vs. Vehicle	0.015		
Amlexanox vs. No-treatment	0.093		
Vehicle vs. No-treatment	–9.16%		
Day 6	115 (38.0%)	107 (35.6%)	35 (36.1%)
Comparison[1]			
Amlexanox vs. Vehicle	0.535		
Amlexanox vs. No-treatment	0.695		
Vehicle vs. No-treatment	–11.52%		
Day 7	154 (50.8%)	159 (52.8%)	47 (48.5%)
Comparison[1]			
Amlexanox vs. Vehicle	0.560		
Amlexanox vs. No-treatment	0.627		
Vehicle vs. No-treatment	–7.06%		

Source: Sponsor's NDA submission (Module 5, Vol.1.3, pages 61 and 132-133). Note that the table is intended to observe efficacy trend, otherwise, a multiplicity adjustment would be needed.
[1] The comparison (p-value) of amlexanox vs. vehicle and amlexanox vs. no-treatment each was based on CMH test adjusting for investigator. The listing for the comparison between vehicle and no-treatment was the lower limit of one-sided 97.5% confidence interval of the treatment difference (i.e., vehicle – no-treatment).

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Table A.4: Patient Enrollment by Investigator – Study 9E03

Investigator ID (Last name)	# patients randomized	Amlexanox	Vehicle	No-treatment
120	5	2	2	1
121	18	7	7	4
122	23	9	10	4
123	14	6	5	3
124	30	12	12	6
125	28	11	12	5
126	35	14	14	7
127	30	12	12	6
128	2	0	1	1
129	35	14	14	7
130	35	14	14	7
131	29	11	12	6
132	32	12	13	7
133	10	4	4	2
134	28	11	12	5
135	10	4	4	2
136	7	2	3	2
501	30	12	12	6
Total	401	157	163	81

Source: Sponsor's electronic SAS data sets at location of \\cdsesub1\n21727\n_000.

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Table A.5: Demographic and Baseline Characteristics (ITT) – Study 9E03

Variable	Amlexanox (n = 157)	Vehicle (n = 163)	No-treatment (n = 81)	p-value
Gender				
Female	105 (66.9%)	93 (57.1%)	58 (71.6%)	0.05
Male	52 (33.1%)	70 (42.9%)	23 (28.4%)	
Age				
Mean (s.d.)	32.26 (12.68)	31.70 (12.94)	30.51 (11.62)	0.595
Median	28	28	27	
Min – max	12 – 67	13 – 74	12 – 78	
Distribution				
≥ 12 and < 18	12 (7.6%)	11 (6.7%)	4 (4.9%)	
≥ 18 and < 65	142 (90.4%)	147 (90.2%)	76 (93.8%)	
≥ 65	3 (1.9%)	5 (3.1%)	1 (1.2%)	
Race				
Caucasian	126 (80.3%)	141 (86.5%)	70 (86.4%)	0.485
Hispanic	17 (10.8%)	12 (7.4%)	6 (7.4%)	
Black	5 (3.2%)	2 (1.2%)	3 (3.7%)	
Asian	8 (5.1%)	8 (4.9%)	1 (1.2%)	
Other	1 (0.6%)	0	1 (1.2%)	
Weight (kg)				
Mean (s.d.)	71.71 (17.41)	71.87 (17.61)	72.06 (18.20)	0.989
Median	69.90	67.85	68.90	
Min – max	38.00 – 160.2	28.20 – 118.0	43.09 – 119.8	
Height (cm)				
Mean (s.d.)	166.0 (12.24)	168.3 (12.04)	166.6 (13.65)	0.236
Median	165.0	168.5	167.0	
Min – max	130 – 198	130 – 198	127 – 196	
Ulcer size (mm^2)				
Mean (s.d.)	10.19 (10.88)	12.38 (14.24)	9.07 (8.58)	0.088
Median	7.00	8.00	6.00	
Min – max	0.25 – 70	0.25 – 80	0.5 – 36	

Source: Sponsor's NDA submission (Module 5, Vol.1.9, pages 90 and 110) and sponsor's electronic SAS data set (demog.xpt) at location of \\cdsesub1\n21727\n_000.

Table A.6: Number (%) of Patients with Complete Ulcer Healing Over Time (ITT) – Study 9E03

Time	Amlexanox (n = 157)	Vehicle (n = 163)	No-treatment (n = 81)
Day 3	14 (8.9%)	9 (5.5%)	4 (4.9%)
Comparison[1]			
Amlexanox vs. Vehicle	0.260		
Amlexanox vs. No-treatment	0.304		
Vehicle vs. No-treatment	–6.8%		
Day 4	36 (22.9%)	25 (15.3%)	13 (16.0%)
Comparison[1]			
Amlexanox vs. Vehicle	0.093		
Amlexanox vs. No-treatment	0.248		
Vehicle vs. No-treatment	–11.4%		
Day 5	76 (48.4%)	58 (35.6%)	23 (28.4%)
Comparison[1]			
Amlexanox vs. Vehicle	0.026		
Amlexanox vs. No-treatment	0.005		
Vehicle vs. No-treatment	–5.6%		
Day 6	94 (59.9%)	81 (49.7%)	34 (42.0%)
Comparison[1]			
Amlexanox vs. Vehicle	0.087		
Amlexanox vs. No-treatment	0.008		
Vehicle vs. No-treatment	–5.8%		
Day 7	113 (72.0%)	102 (62.6%)	42 (51.9%)
Comparison[1]			
Amlexanox vs. Vehicle	0.074		
Amlexanox vs. No-treatment	0.001		
Vehicle vs. No-treatment	–2.6%		

Source: Sponsor's NDA submission (Module 5, Vol.1.9, page 116). Note that the table is intended to observe efficacy trend, otherwise, a multiplicity adjustment would be needed.

[1] The comparison (p-value) of amlexanox vs. vehicle and amlexanox vs. no-treatment each was based on CMH test adjusting for investigator. The listing for the comparison between vehicle and no-treatment was the exact lower limit of one-sided 97.5% confidence interval of the treatment difference (i.e., Vehicle – No-treatment) using StatXact V.5.0.

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Table A.7: Percentage of Patients with Complete Ulcer Healing on Day 5 by Investigational Site – Study 1U106

Investigator ID (Last name)	# patients randomized	Amlexanox	Vehicle	No-treatment
125	11	0/4 (0%)	2/6 (33%)	1/1 (100%)
126	31	7/14 (50%)	4/13 (31%)	1/4 (25%)
127	33	6/15 (40%)	1/14 (7%)	1/4 (25%)
129	27	6/12 (50%)	3/11 (27%)	1/4 (25%)
131	28	2/12 (17%)	3/12 (25%)	2/4 (50%)
132	13	1/6 (17%	0/5 (0%)	1/2 (50%)
135	49	5/21 (24%)	5/21 (24%)	3/7 (43%)
159	46	5/19 (26%)	4/20 (20%)	2/7 (29%)
160	34	4/15 (27%)	1/14 (7%)	0/5 (0%)
161	44	6/19 (32%)	4/19 (21%)	2/6 (33%)
162	58	11/24 (46%)	5/25 (20%)	1/9 (11%)
163	1	NA	1/1 (100%)	NA
166	6	2/2 (100%)	1/3 (33%)	0/1 (0%)
168	12	0/6 (0%)	1/5 (20%)	0/1 (0%)
169	23	3/10 (30%)	2/10 (20%)	0/3 (0%)
170	32	0/14 (0%)	0/14 (0%)	1/4 (25%)
171	6	2/3 (67%)	1/3 (33%)	NA
172	15	2/6 (33%)	2/7 (29%)	1/2 (50%)
173	27	2/12 (17%)	2/11 (18%)	0/4 (0%)
174	49	7/21 (33%)	4/21 (19%)	1/7 (14%)
175	49	9/21 (43%)	11/21 (52%)	1/7 (14%)
177	12	0/6 (0%)	1/4 (25%)	1/2 (50%)
178	21	3/9 (33%)	3/9 (33%)	0/3 (0%)
180	51	7/22 (32%)	5/22 (23%)	0/7 (0%)
181	4	0/1 (0%)	0/2 (0%)	1/1 (100%)
182	1	NA	0/1 (0%)	NA
183	18	2/9 (22%)	0/7 (0%)	0/2 (0%)
Total	701	92/303 (30.4%)	66/301 (21.9%)	21/97 (21.6%)

Source: Sponsor's electronic SAS data sets at location of \\cdsesub1\n21727\n_000.

Table A.8: Percentage of Patients with Complete Ulcer Healing on Day 5 by Investigational Site – Study 9E03

Investigator ID (Last name)	# patients randomized	Amlexanox	Vehicle	No-treatment
120	5	0/2 (0%)	0/2 (0%)	1/1 (100%)
121	18	4/7 (57%)	4/7 (57%)	2/4 (50%)
122	23	3/9 (33%)	3/10 (30%)	1/4 (25%)
123	14	4/6 (67%)	3/5 (60%)	1/3 (33%)
124	30	5/12 (42%)	5/12 (42%)	1/6 (17%)
125	28	7/11 (64%)	3/12 (25%)	2/5 (40%)
126	35	9/14 (64%)	10/14 (71%)	2/7 (29%)
127	30	9/12 (75%)	6/12 (50%)	1/6 (17%)
128	2	NA	0/1 (0%)	0/1 (0%)
129	35	6/14 (43%)	4/14 (29%)	1/7 (14%)
130	35	4/14 (29%)	2/14 (14%)	0/7 (0%)
131	29	4/11 (36%)	3/12 (25%)	3/6 (50%)
132	32	4/12 (33%)	4/13 (31%)	3/7 (43%)
133	10	2/4 (50%)	3/4 (75%)	2/2 (100%)
134	28	5/11 (45%)	3/12 (25%)	1/5 (20%)
135	10	2/4 (50%)	1/4 (25%)	0/2 (0%)
136	7	0/2 (0%)	0/3 (0%)	0/2 (0%)
501	30	8/12 (67%)	4/12 (33%)	2/6 (33%)
Total	401	76/157 (48.4%)	58/163 (35.6%)	23/81 (28.4%)

Source: Sponsor's electronic SAS data sets at location of \\cdsesub1\n21727\n_000.

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Table A.9: Percentage of Patients with Complete Ulcer Healing on Day 5 By the Number of Treated Ulcer

ITT Analysis	Amlexanox	Vehicle	No-treatment
Study 1U106			
Overall, n (%)	92/303 (30.4%)	66/301 (21.9%)	21/97 (21.6%)
One treated ulcer	80/219 (36.5%)	59/231 (25.5%)	19/68 (27.9%)
Two treated ulcers	10/58 (17.2%)	4/50 (8.0%)	1/21 (4.8%)
Three treated ulcers	2/26 (7.7%)	3/20 (15.0%)	1/8 (12.5%)
Study 9E03			
Overall, n(%)	76/157 (48.4%)	58/163 (35.6%)	23/81 (28.4%)
Source: Sponsor's electronic SAS data sets at location of \\cdsesub1\n21727\n_000.			

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Table A.10: Subgroup Results of Complete Ulcer Healing Rate on Day 5 (ITT) Study 1U106

Subgroup	Amlexanox (n = 303)	Vehicle (n = 301)	No-treatment (n = 97)
Overall	92/303 (30.4%)	66/301 (21.9%)	21/97 (21.6%)
Age			
Pediatric (12 – 17 years)	11/37 (29.7%)	13/49 (26.5%)	4/12 (33.3%)
Adult (18 – 64 years)	78/263 (29.7%)	53/248 (21.4%)	17/84 (20.2%)
Geriatric (65 and older)	3/3 (100%)	0/4 (0%)	0/1 (0%)
Gender			
Male	30/107 (28.0%)	16/99 (16.2%)	7/37 (18.9%)
Female	62/196 (31.6%)	50/202 (24.8%)	14/60 (23.3%)
Race			
Caucasian	83/265 (31.3%)	55/259 (21.2%)	16/77 (20.8%)
Black	2/6 (33.3%)	2/7 (28.6%)	1/2 (50%)
Hispanic	5/21 (23.8%)	4/22 (18.2%)	1/11 (9.1%)
Asian	0/5 (0%)	3/7 (42.9%)	1/2 (50%)
Other	2/6 (33%)	2/6 (33%)	2/5 (40%)
Number of treated ulcers			
One	80/219 (36.5%)	59/231 (25.5%)	19/68 (27.9%)
Two	10/58 (17.2%)	4/50 (8.0%)	1/21 (4.8%)
Three	2/26 (7.7%)	3/20 (15.0%)	1/8 (12.5%)
Baseline ulcer size			
0 – 20 mm^2	85/229 (37.1%)	54/230 (23.5%)	20/79 (25.3%)
more than 20 mm^2	7/74 (9.5%)	12/71 (16.9%)	1/18 (5.6%)
Baseline pain score			
0 – 50 mm	63/182 (34.6%)	39/182 (21.4%)	16/60 (26.7%)
> 50 mm	29/116 (25.0%)	27/118 (22.9%)	5/34 (14.7%)
Missing	0/5 (0%)	0/1 (0%)	0/3 (0%)

Source: Sponsor's NDA submission (dated 3/15/04, Module 5, Vol.5.1, pages 3-4) and sponsor's electronic SAS data set (LOGIT.xpt) at location of \\cdsesub1\n21727\n_000.

Table A.11: Subgroup Results of Complete Ulcer Healing Rate on Day 5 (ITT) Study 9E03

Subgroup	Amlexanox (n = 157)	Vehicle (n = 163)	No-treatment (n = 81)
Overall	76/157 (48.4%)	58/163 (35.6%)	23/81 (28.4%)
Age			
Pediatric (12 – 17 years)	3/12 (25.0%)	3/11 (27.3%)	3/4 (75.0%)
Adult (18 – 64 years)	71/142 (50.0%)	54/147 (36.7%)	20/76 (26.3%)
Geriatric (65 and older)	2/3 (66.7%)	1/5 (20.0%)	0/1 (0%)
Gender			
Male	22/52 (42.3%)	21/70 (30.0%)	4/23 (17.4%)
Female	54/105 (51.4%)	37/93 (39.8%)	19/58 (32.8%)
Race			
Caucasian	63/126 (50.0%)	51/141 (36.2%)	20/70 (28.6%)
Black	2/5 (40.0%)	1/2 (50.0%)	0/3 (0%)
Hispanic	7/17 (41.2%)	3/12 (25.0%)	2/6 (33.3%)
Asian	4/8 (50.0%)	3/8 (37.5%)	0/1 (0%)
Other	0/1 (0%)	NA	1/1 (100%)
Number of treated ulcers			
One	76/157 (48.4%)	58/163 (35.6%)	23/81 (28.4%)
Two	NA	NA	NA
Three	NA	NA	NA
Baseline ulcer size			
0 – 20 mm^2	73/140 (52.1%)	56/138 (40.6%)	21/74 (28.4%)
more than 20 mm^2	3/17 (17.7%)	2/25 (8.0%)	2/7 (28.6%)
Baseline pain score			
0 – 50 mm	59/121 (48.8%)	48/135 (35.6%)	17/62 (27.4%)
> 50	17/36 (47.2%)	10/28 (35.7%)	6/18 (33.3%)
Missing	NA	NA	0/1 (0%)

Source: Sponsor's NDA submission (dated 3/15/04, Module 5, Vol.5.1, page 6) and electronic SAS data set (Diary_p.xpt) at location of \\cdsesub1\n21727\n_000.

Table A.12: Mean (S.D.) of Baseline Ulcer Size (in mm^2) by Complete Ulcer Healing Rate on Day 5 (ITT) Over Gender and Treatment Group – Study 1U106

Gender, n Mean (s.d.)	Complete Ulcer Healing	Amlexanox	Vehicle	No-treatment	Total
Female	**No**	134 18.1 (17.20)	152 17.7 (19.22)	46 15.2 (21.28)	332
	Yes	62 8.1 (6.52)	50 11.3 (17.11)	14 5.2 (5.38)	126
	Total	196 14.9 (15.39)	202 16.1 (18.89)	60 12.8 (19.24)	458
Male	**No**	77 18.3 (17.89)	83 12.1 (13.05)	30 20.1 (24.83)	190
	Yes	30 6.5 (6.24)	16 9.7 (9.53)	7 8.6 (9.59)	53
	Total	107 15.0 (16.38)	99 11.7 (12.54)	37 17.9 (23.08)	243

Source: Sponsor's electronic SAS data sets at location of \\cdsesub1\n21727\n_000.

Table A.13: Mean (S.D.) of Baseline Ulcer Size (in mm^2) by Complete Ulcer Healing Rate on Day 5 (ITT) Over Gender and Treatment Group – Study 9E03

Gender, n Mean (s.d.)	Complete Ulcer Healing	Amlexanox	Vehicle	No-treatment	Total
Female	**No**	51 12.2 (11.92)	56 13.6 (13.13)	39 8.9 (8.42)	146
	Yes	54 8.1 (8.97)	37 7.1 (6.31)	19 8.3 (7.83)	110
	Total	105 10.1 (10.66)	93 11.0 (11.36)	58 8.7 (8.17)	256
Male	**No**	30 13.6 (13.76)	49 17.2 (19.30)	19 11.0 (10.29)	98
	Yes	22 5.9 (4.37)	21 7.2 (7.77)	4 5.0 (3.77)	47
	Total	52 10.4 (11.42)	70 14.2 (17.27)	23 9.9 (9.69)	145

Source: Sponsor's electronic SAS data sets at location of \\cdsesub1\n21727\n_000.

Table A.14: Complete Ulcer Healing Rate on Day 5 (ITT) Over Gender, the Number of Treated Ulcers and Treatment Group – Study 1U106

Gender	Complete Ulcer Healing	Amlexanox			Vehicle			No-treatment		
		1	2	3	1	2	3	1	2	3
Female	**No**	88 (62.9%)	31 (77.5%)	15 (93.8%)	110 (71.0%)	28 (90.3%)	14 (87.5%)	33 (71.7%)	9 (90%)	4 (100%)
	Yes	52 (37.1%)	9 (22.5%)	1 (6.2%)	45 (29%)	3 (9.7%)	2 (12.5%)	13 (28.3%)	1 (10%)	0
	Total	140	40	16	155	31	16	46	10	4
Male	**No**	51 (64.6%)	17 (94.4%)	9 (90%)	62 (81.6%)	18 (94.7%)	3 (75%)	16 (72.7%)	11 (100%)	3 (75%)
	Yes	28 (35.4%)	1 (5.6%)	1 (10%)	14 (18.4%)	1 (5.3%)	1 (25%)	6 (27.3%)	0	1 (25%)
	Total	79	18	10	76	19	4	22	11	4

Source: Sponsor's electronic SAS data sets at location of \\cdsesub1\n21727\n_000.

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-727

Microbiology Review(s)

Product Quality Microbiology Review
Review for HFD-540

17 SEPTEMBER 2004

NDA: 21-727

Drug Product Name
Proprietary: OraDisc A
Non-proprietary: Amlexanox mucoadhesive patch
Drug Product Priority Classification: S

Review Number: 1

Subject of this Review
Submission Date: 4 December 2003
Receipt Date: 12 December 2003
Consult Date: 12 July 2004
Date Assigned for Review: 3 August 2004

Submission History (for amendments only)
Date(s) of Previous Submission(s): N/A
Date(s) of Previous Micro Review(s): N/A

Applicant/Sponsor
Name: Access Pharmaceuticals, Inc.
Address: 2600 Stemmons Frwy, Suite 176, Dallas TX 75207
Representative: Amy Campbell
Telephone: 214-905-5100

Name of Reviewer: Bryan S. Riley, Ph.D.

Conclusion: Recommend Approval

Product Quality Microbiology Data Sheet

A. 1. **TYPE OF SUPPLEMENT:** N/A

2. **SUPPLEMENT PROVIDES FOR:** N/A

3. **MANUFACTURING SITE:** [

]

4. **DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY:** Mucoadhesive Patch for oral mucosa (0.5 inch dia., 35-45 mg), 2 mg Amlexanox/patch

5. **METHOD(S) OF STERILIZATION:** N/A

6. **PHARMACOLOGICAL CATEGORY:** Aphthous Ulcers

B. **SUPPORTING/RELATED DOCUMENTS:** N/A

C. **REMARKS:** none

filename: 21727.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability – This submission is recommended for approval on the basis of product quality microbiology.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology – The drug product is a non-sterile patch designed to be applied to the oral mucosa.

B. Brief Description of Microbiology Deficiencies – N/A

C. Assessment of Risk Due to Microbiology Deficiencies – N/A

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block
Bryan S. Riley, Ph.D. (Microbiology Reviewer)
Microbiology Supervisor

C. CC Block
N/A

2 Page(s) Withheld

✓ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

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Bryan Riley
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James McVey
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MICROBIOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-727

Clinical Pharmacology and Biopharmaceutics Review

NDA 21-727
Amlexanox 2 mg Patch, DFS Copy

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 21-727/N000

Brand Name:	OraDisc™A
Generic Name:	Amlexanox 2 mg, Mucoadhesive Patch
Dosage Form:	Mucoadhesive Patch
Dosage Strength:	2 mg
Indication:	Treatment of Aphthous Ulcers
NDA Type:	Original NDA
Submission Date(s):	12/04/03, 03/04/04, 08/13/2004
Sponsor:	Access Pharmaceuticals, Inc.
Reviewer:	Chandra S. Chaurasia, Ph.D.
Acting Team Leader:	Arzu Selen, Ph.D.
OCPB Division:	DPE III (HFD-880)
OND Division:	ODE V (HFD-540)

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1. EXECUTIVE SUMMARY

Amlexanox is a benzopyrano-bipyridine carboxylic acid derivative with antiinflammatory and antiallergic properties. It is approved in the United States as an oral paste in 5% strength (Aphthasol) for topical use in aphthous ulcers in adult population with normal immune systems (NDA 20-511, 12/17/96, Glaxo Smith Kline). The drug is available in Japan as an oral tablet (25 mg and 50 mg strengths) for the treatment of asthma and allergic rhinitis, approved in 1987, and as a 0.25% nasal douche and ophthalmic solution for the treatment of local allergic symptoms.

OraDisc (Amlexanox 2mg, Mucoadhesive Patch) is a topical solid patch formulation that is to be applied to the oral mucosa. Following administration, the patch slowly erodes on the mucosa, releasing the active agent to the area of the aphthous ulcer. Amlexanox from the eroded patch is expected to be swallowed by the subject over the course of 1 to 2 hours. The swallowed amlexanox is absorbed from the gastrointestinal tract to produce systemic serum levels of amlexanox.

To support the clinical safety and efficacy of OraDisc, the Sponsor has conducted pivotal Phase 1 single dose (Study AP-C-1U107) and Phase 3 (Study AP-C-1U-106) multiple dose studies. In addition, clinical safety data of amlexanox from the oral paste and tablet formulations are available.

The basic pharmacokinetic characteristics of amlexanox were determined in the studies with amlexanox tablets. Systemically absorbed amlexanox is metabolized by hydroxylation to form the M-1 metabolite and some unidentified conjugates. M-1 metabolite concentrations in serum were approximately 10% of the levels of amlexanox. There was no evidence of any accumulation of amlexanox or M-1 with multiple dosing.

Following topical administration of OraDisc patch, amlexanox exhibits systemic absorption. After normalization for dose, the AUC0-24 values for OraDisc were similar to those for amlexanox tablets and for Aphthasol paste, indicating similar systemic exposure. The dose-normalized Cmax values tended to be lower for the patch than for the Aphthasol paste. The terminal half-life values were very similar for each formulation.

It is noted that the paste is approved for adult population only. In the pivotal Phase 3 trial, efficacy and safety was determined also in adolescents (n=37/303 or 12%). In the pharmacokinetic subset of studyAP-C-1U106, 31 subjects were treated with OraDisc. Of these, only 3 were in the age range of 12-18 years. Thus, the number of subjects in the adolescent population is too small to allow a statistical comparison of adult and adolescent exposure values. However, as there were no efficacy or safety differences, pharmacokinetic data from the adolescents which were similar to those from the adult population group, are considered adequate, pharmacokinetic differences would be highly unlikely between the adolescents and the adults for the amlexanox oral patch formulation.

Furthermore, the Sponsor has provided dissolution release profile of OraDisc using USP apparatus 2, at [ ] rpm in 900 mL of the artificial saliva medium. The proposed specification is NLT[ ] within 60 minutes. The reported % release of the OraDisc 2 mg patches are [ ] (range [ ] and [ ] ([ ]), at [ ] and 60 minutes, respectively. The Agency requests the Sponsor to set an interim dissolution specification of NLT(Q) [ ] at 60 minutes.

1.1 Recommendations:

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the information submitted in support of the amlexanox mucoadhesive patch, 2 mg and found it to be acceptable for meeting the requirements of 21CFR320. The Sponsor is requested to set an interim dissolution specification of NLT(Q) [ ] of the labeled content of the drug to be dissolved in 60 minutes.

1.2 Phase IV Commitment: None requested at this time.

1.3 Summary of Important Clinical Pharmacology and Biopharmaceutics Findings

The Sponsor, Access Pharmaceuticals, is seeking approval of OraDisc (amlexanox mucoadhesive patch 2mg) for treatment of [ ] aphthous ulcers in adults and adolescents 12 years of age and older. The NDA 21-727 is a 505 (b)(2) application. The approved product Amlexanox Oral Paste 5% (NDA 21-511) has identical dosing regimen and indication for adult population only. It is noted that the 2 mg amount of amlexanox in each OraDisc corresponds to the average amount of amlexanox in one dab of amlexanox paste, 5%. The frequency of 4 times per day is also identical to the frequency that was proved efficacious for the amlexanox paste.

In support of this application the sponsor has submitted the following clinical studies:

1. **Protocol AP-C-1U107:** A phase 1 study to investigate the single dose pharmacokinetic characteristics of OraDisc 2 mg.
2. **Protocol AP-C-1U106:** A phase 3 study to determine the safety and efficacy, and to measure serum levels of amlexanox after multiple application of OraDisc 2 mg patches.

The phase 1 study AP-C-1U107 was conducted to investigate the pharmacokinetics and safety of amlexanox OraDisc, 2 mg in adult population (≥18 years of age, N=18) with minor aphthous ulcers after a single application to 1-3 aphthous ulcers. Mean serum PK parameters are presented in Table 1 below.

Table 1. Mean Pharmacokinetic Parameters Phase 1 Study AP-C-1U107

Parameter	One Patch 2 mg	Two Patches 4 mg	Three Patches 6 mg
Cmax (ng/mL)	N=14	N=1	N=3
Mean ±SD	45.4±39.6	138	168.3±191.5
Median (range)	39.8 [ ]		79.9 [ ]
Tmax (hr)	N=13	N=1	N=3
Mean ±SD	2.8±1.7	3	3.0±1.0
Median (range)	2 [ ]		3 [ ]
T_{lag} (hr)	N=13	N=1	N=3
Mean ±SD	1.0±0.6	1	1.0±0.9
Median (range)	1 [ ]		0.5 [ ]
AUC_{0-24} (ng·hr/mL)	N=14	N=1	N=3
Mean ±SD	258±238	475	605±356
Median (range)	226 [ ]		584 [ ]
$T_{1/2}$ (hr)	N=7	N=1	N=3
Mean ±SD	4.5±2.0	3.2	8.8±3.5
Median (range)	4.5 [ ]		10.3 [ ]

The highest observed serum concentration of amlexanox for a subject who received one patch was [ ] ng/mL, and the lowest measurable Cmax was [ ] ng/mL. The mean concentration was 45.4 ± 39.6 (range [ ] mL, N=14). The mean values for AUC_{0-24} for one and three OraDiscs were 258 ± 238 and 605 ±356 ng·hr/mL, respectively.

The Cmax value for the subject who received 2 OraDisc was 138 ng/mL 3-hr post-dose. However, no statistical inference could be made due to limited number of subject (N=1). As

indicated in the results, there is a substantial inter-subject variability in the Cmax values presumably due to individual variation in the amount and rate of systemic absorption.

Based on the reported Tlag (0-1 hr) and mean Tmax (~ 3 hours), there appears to be no or little absorption of amlexanox rapidly and directly through the aphthous ulcers. The lag time and Tmax values indicate a slow erosion of OraDisc, and a slow systemic absorption of amlexanox from the drug product.

Considering the AUC data from the one and three OraDisc treatment, there is no trend of nonlinearity over the range of 2 to 6 mg dose, however, the number of subjects (N=3) in the 6 mg dose (i.e., 3 OraDiscs) is too small to reach any conclusion on the dose proportionality.

The secondary objective of this study was to collect information on the retention and resorption properties of OraDisc when applied to aphthous ulcers. Following application, the patch slowly erodes in the mouth, generally disappearing entirely in 50-80 minutes. During this process, the patient may feel some type of debris due to patch erosion.

The phase 3 study AP-C-1U106 was evaluator-blinded, randomized, parallel-group study with the following objectives:

- To determine the effect of amlexanox formulated as OraDisc on the healing rate of recurrent aphthous ulcers patients presenting with recurrent minor aphthous ulcers.
- To evaluate the safety of amlexanox OraDisc by determining the frequency of treatment-emergent adverse events.
- To measure serum levels of amlexanox after multiple applications of OraDisc.

The study included male or females of at least 12 years of age with a reported history of recurrent minor aphthous ulcers taking 5 days or more to resolve. Patients were randomized to 3:3:1 to active patches, vehicle patches or no-treatment. The "no-treatment' arm was included in order to demonstrate that the vehicle patch did not have a worsening, irritating effect on the aphthous ulcers.

Patches were applied four times a day (after each meal and at bed time) directly over the designated ulcer(s) for 7 days or until all treated ulcers healed, whichever occurred first. Up to a maximum of 3 ulcers were treated per patient. Blood samples were collected on Day 4 prior to the first patch application, and two hours after the first patch application. A total of 152 samples were collected from 77 patients at 7 study centers. Of these samples, 60 were obtained from 31 patients in the Amlexanox OraDisc group. All but 2 provided both pre-dose and 2-hour post-dose samples. Sixty-six samples were obtained from 33 patients and 26 samples were obtained from 13 patients from the vehicle patch and no treatment groups, respectively. Of the 31 patients treated with OraDisc only 3 were in the age range of 12 to 18 years. No amlexanox was detected in any of the samples taken from patients in the vehicle and no treatment groups reported at the LOQ level of – ng/mL. The PK results obtained from the OraDisc-treated group is summarized in the Table 2. below:

Table 2. Mean Pharmacokinetic Parameters, Phase 3 Study AP-C-1U106

Treatments	Amlexanox Serum Concentrations (ng/mL)	
	Prior to First Dose on Day 4	Two hours after First Dose on Day 4
All Patients		
Mean SD	16.0 ±31.7 (N=31)	20.9 ±24.1 (N=29)
Median (Range)	6.6 [ ]	14.8 [ ]
Pediatric Patients (N=3)		
	3.7± 5.2 [ ]	13.5±12.3 [ ]
Patients Treated with One Patch, 4x daily		
Mean SD	9.8±16.5 (24)	15.8±16.4 (N=24)
Median (Range)	5.6 [ ]	11.5 [ ]
Patients Treated with Two Patches, 4x daily		
Mean SD	43.9±68.5 (N=5)	44.4±42.7 (N=5)
Median (Range)	10.0 [ ]	35.4 [ ]
Patients Treated with Three Patches, 4x daily		
Mean SD	20.4 (N=2)	18.6 (N=2)
Median (Range)	20.4 [ ]	18.6 [ ]

As noted in the Table above, prior to first dose on Day 4, the maximum pre-dose concentrations (Cmin) were [ ] ng/mL for subjects who applied 1, 2 and 3 patches, respectively. The corresponding maximum 2-hr concentrations after first dose on Day 4 were [ ] ng/mL. The inter-subject variability was high in all groups. Furthermore, because of low number of subjects in the 2 and 3 patch-treatment groups, comparison for dose-proportionality is not possible.

The maximum systemic exposure to amlexanox for subjects (N=24) receiving one patch of OraDisc 4 time daily for 3 days was 79 ng/mL. This is lower than the reported Cmax value for the approved amlexanox product 5% paste (116 ±71.2 ng/mL).

As mentioned above, the number of subjects in the adolescent population is too small (N=3) to give any statistically meaningful conclusion with respect to overall exposure of amlexanox in this population. Nevertheless, the amlexanox concentrations in this group are comparable to the values seen in the adults.

In addition to the above pivotal studies, the firm has provided results of pharmacokinetic data from the following clinical trials:

- Study No. AP-C-9E03; A phase 2/3 investigator-blind, randomized, parallel-group study to determine the effects and serum levels of amlexanox disc 2 mg on the healing of recurrent aphthous ulcers as compared with vehicle discs or no treatment in patients 12 years of age or older.
- Study No. 34,787-110: A phase 1 study to determine the pharmacokinetics of amlexanox after a single topical administration of 100 mg of 5% amlexanox paste to minor aphthous ulcers.
- Study No. BD98-006: A phase 1 study in children 8 to 12 years of age to determine the pharmacokinetics of amlexanox after a single topical administration of 5% amlexanox paste to the oral mucous membrane.

In Study AP-C-9E03 an Early Formulation patch was applied qid for 7 days. Serum levels of amlexanox was determined after 3 full days of treatment before the first application and 1 hour post-dosing on Day 4. As agreed upon between the Sponsor and Agency, the above study AP-C-9E03 is not being considered for approval of this NDA. The PK results from this study have been summarized in the QBR section 2.1 for supportive purpose only.

Study No. 34,787-110 and BD. 98-006 were reviewed by the Agency as part of the NDA 20-511 and IND [ ], respectively. The PK results of these studies are summarized in the Table 4 below. PK results from the amlexanox oral tablet are also provided for reference purpose.

Single-Dose Pharmacokinetics of amlexanox from 5% oral paste and tablet formulations

Study No	Formulation/Dosage Form	Dose Used in Study	AUC_{0-24} (ng· hr/mL/mg)	Cmax (ng/mL/mg) [ng/mL]	$T_{1/2}$
34,787-110 Adults Healthy Subjects (19-50 yrs)	Aphthasol Paste 5%	5 mg	629 ± 366 (N=12)	117 ± 71(N=12)	4.1
Phase 1, Healthy Pediatrics (8-12 yrs)	Aphthasol Paste 5%	5 mg	1026 ± 550(AUC_{0-8}) 205*	469 ± 202 93*	1.2
AA-673/X-108/Adults, healthy subjects (31-48 yrs)	Tablets/Oral	12.5 mg 25 mg 50 mg 100 mg	95* 163* 268* 148*	39.2* 45.6* 95.6* 28.4*	-

**Normalized to 1 mg Amlexanox*

Dissolution:
The applicant has conducted dissolution testing using the USP apparatus in artificial saliva medium. The Sponsor's proposed specification is NLT[ ], of the active ingredient released within 60 minutes.

Since product is designed to erode in the mouth after approximately one hours, and the average time for almost complete erosion of OraDisc patch is [ ] minutes, the firm's proposed specification of NLT [ ] active release within 60 min appears reasonable.

Chandra S. Chaurasia, Ph.D. _____ Date: _____
Clinical Pharmacology and Biopharm Reviewer
Division of Pharmaceutical Evaluation III

RD/FT Initialed by Arzu Selen, Ph.D.. _____ Date: _____
Deputy Director, DPE-III/
Acting Team Leader HFD880

CC: NDA 21-727, HFD-850 (P. Lee), HFD-540 (J. Smith), HFD-880 (J. Lazor, A. Selen)

2. Question Based Review

2.1 General Attributes of Amlexanox

2.1.1 What regulatory background or history information contributes to the assessment of the clinical pharmacology and biopharmaceutics of this drug?

This application is based on the following features that would support an NDA filing under the section 505(b) (2) of the Federal Food Drug and Cosmetic Act.

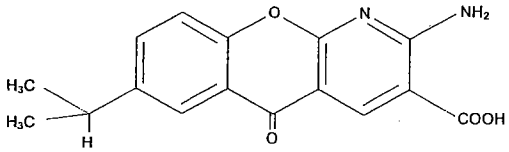
Amlexanox Oral Paste 5% is approved in the United States for topical use in aphthous ulcers in **adult population** with normal immune systems (NDA 20-511, 12/17/96, Glaxo Smith Kline). The drug is available in Japan as an oral tablet for the treatment of asthma, and as a nasal douche and ophthalmic solution for the treatment of local allergic symptoms.

The primary focus of this NDA is to establish efficacy and safety of the oral mucoadhesive patch formulation in adolescent and adult populations. The 2 mg amount of amlexanox in each OraDisc corresponds to the average amount of amlexanox in one dab of amlexanox paste, 5%. The frequency of 4 times per day is also identical to the frequency that was proved efficacious for the amlexanox paste.

To establish systemic exposure the Sponsor has provided PK results of a single dose Phase1 and a multiple dose Phase 3 studies.

2.1.2 What are the highlights of the chemistry and physical-chemical properties of the drug substance, and the formulation of the product?

OraDisc™A is a mucoadhesive patch that contains 2 mg of amlexanox as part of a multi-layer patch consisting of ethylcellulose, FD&C Blue #1, FD&C Red #40, hydroxyethylcellulose, hypromellose, methylparaben, modified starch, polycarbophil, povidone, propylene glycol, propylene glycol monostearate, purified water, sodium benzoate, sodium carboxymethylcellulose
Chemical Name: 2-amino-7-isopropyl-5-oxo-5H-[1] benzopyrano [2, 3-b] pyridine-3-carboxylic acid.
Structural formula



Empirical Formula: $C_{16}H_{14}N_2O_4$
Molecular Weight: 298.30
Physicochemical Properties: Amlexanox is an odorless, white to yellowish-white crystalline powder insoluble in water.

2.1.3. What are the proposed mechanism of action and therapeutic indication of amlexanox?

Mechanism of Action: The mechanism of action by which amlexanox accelerates healing of aphthous ulcers is unknown. *In vitro* studies have demonstrated amlexanox to be a potent inhibitor of the formation and/or release of inflammatory mediators (histamine and leukotrienes) from mast cells, neutrophils, and mononuclear cells.

Indication: Amlexanox OraDisc™ is indicated for the treatment of [ ] aphthous ulcers in adults and adolescents 12 years of age and older.

2.1.4 What is the proposed dosage and route of administration?

Dosage and Administration: The proposed dose for OraDisc™ is one patch four times daily, preferably following oral hygiene after breakfast, lunch, dinner, and [ ] before bedtime. In case of multiple ulcers, application of one OraDisc™ patch to each ulcer is indicated. Multiple patches may be used at one time. Use of the medication should be continued until the ulcer heals.

2.2. General Clinical Pharmacology

2.2.1 What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

The Sponsor conducted two pivotal studies to support the clinical pharmacology aspects of the OraDisc patch.

The phase I study (no. AP-C-1U107) was conducted to investigate the pharmacokinetic and safety characteristics of Amlexanox OraDisc 2 mg in 18 subjects with minor aphthous ulcers after a single application to 1-3 aphthous ulcers. In addition, the study also collected information on the retention and resorption properties of OraDisc when applied to the aphthous ulcers.

The phase III study (No. AP-C-1U106) was a multi-center, multi-dose, evaluator-blinded, parallel-group, vehicle-controlled, no-treatment-controlled, parallel-group study in male or females at least 12 years of age in general good health and with a reported history of recurrent minor aphthous ulcers taking 5 days or more to resolve. The study was conducted to determine the effect of amlexanox formulated as OraDisc on the healing rate of recurrent aphthous ulcers patients presenting with recurrent minor aphthous ulcers. A subset of the study population was used to measure serum levels of amlexanox after multiple applications of OraDisc.

2.2.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology and clinical studies?

As this NDA is a line extension of the approved amlexanox 5% paste, with the same indications and dosing regimen, same endpoints were studied.

2.2.3 Are the active moiety in the plasma or other biological fluid appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, the Sponsor measured the amlexanox in clinical pharmacology studies. See Analytical section for more details.

2.2.4. Exposure-response evaluations

Since amlexanox was already approved as a paste, information included in this NDA is specific to characterization of the product in adolescent and adult patients.

2.2.4.1 What are the characteristics of the exposure-response relationships for efficacy?

Based on NDA 20-511 for amlexanox paste, no new exposure-response information has been submitted for the current mucoadhesive patch dosage form. The pharmacokinetics of OraDisc are consistent with the pharmacokinetics of Aphthasol. The exposure-response relationships for efficacy are expected to be comparable to those seen with Aphthasol.

2.2.4.2 What are the characteristics of the exposure-response relationships for safety?

A direct assessment of the exposure-response relationship for safety was not contained in this NDA.

2.2.4.3 Does this drug prolong the QT or QTc interval?

Amlexanox is not known to affect the QT interval.

2.2.4.4 Are the dose and dosing regimen consistent with the known relationship between dose-concentration-response, and are there any unresolved dosing or administration issues?

As this is a line extension with no changes in either dosing or indications, this does not apply here.

2.2.5 What are the pharmacokinetic characteristics of the drug and its metabolite?

2.2.5.1 What are the single dose and multiple dose pharmacokinetic parameters?

Single Dose PK Study No. AP-C-1U107
Mean serum for PK parameters are presented in Table 1 above under Summary of Important Clinical Pharmacology and Biopharmaceutics Findings in Section 1 of this review. The highest observed serum concentration of amlexanox for a subject who received one patch was [ ] ng/mL, and the lowest measurable Cmax was [ ] ng/mL. The mean concentration was 46.4 ± 39.6 (range [ ] ng/mL, N=14).
Of the 14 subjects who received one OraDisc, one subject (#13) did not have measurable concentration of amlexanox at any sampling time, and 4 subjects (#8, 14, 17 and 18) had concentrations of 10 ng/mL or less at all sampling times. The mean Cmax and AUC0-24 of amlexanox in 13 subjects with measurable levels, were 45.4 ng/mL (range [ ] and 258 ng.hr/mL (range [ ], respectively.
The Cmax value for the subject who received 2 OraDisc was 138 ng/mL 3-hr post-dose. However, no statistical inference could be made due to limited number of subject (N=1). As

indicated in the results Table, there is a substantial inter-subject variability in the Cmax values presumably due to individual variation in the amount and rate of systemic abruption. However, the mean Cmax values tended to increase with increasing number of OraDisc applied with a statistically significant difference ($p = 0.027$, two sample t-test) when comparing the Cmax values for one and three OraDiscs.

The mean half-life values were 4.5 ± 2.0 and 8.8 ± 3.5 for subjects who received one or three patches, respectively, the half-life for the one subject who received two patches was 3.2 hr.

Multiple Dose PK Study No. AP-C-1U106
Pharmacokinetic results: No amlexanox was detected in any of the samples taken from patients in the vehicle and no treatment groups reported at the LOQ level of [redacted] ng/mL. The PK results obtained from the OraDisc-treated group is summarized in Table 2 above under Summary of Important Clinical Pharmacology and Biopharmaceutics Findings in Section 1.

Prior to first dose on Day 4, the maximum pre-dose concentrations (Cmin) were [redacted] and [redacted] ng/mL for subjects who applied 1, 2 and 3 patches, respectively. The corresponding maximum 2-hr concentrations after first dose on Day 4 concentrations were [redacted] ng/mL. The maximum systemic exposure to amlexanox for subjects (N=24) receiving one patch of OraDisc 4 time daily for 3 days was 79 ng/mL.

Due to smaller sampling size, with two patch (N=5) and three (N=2) patch treatments, no conclusive observation on a dose-proportionality of systemic availability could be inferred. The inter-subject variability was high in all groups.

2.2.5.2 How does the pharmacokinetics of the drug and its major active metabolites in healthy volunteers compare to that in patients?

Not applicable.

2.2.5.3 What are the characteristics of drug absorption?

Tmax occurred at approximately 3 hr (mean Tmax of 2.8±1.7, 3.0 and 3.0±1.0 hr for one, two and three OraDisc, respectively). Most subjects observed a lag time (T_{lag}) of 0-0.5 hours. A Tlag of 0-1 hour was observed in 9/13 (69%) of the subjects receiving one OraDisc treatment. Based on the reported Tlag (0-1 hr) and mean Tmax (~ 3 hours), there appears to be no or little absorption of amlexanox rapidly and directly through the aphthous ulcers. The lag time and Tmax values indicate a slow erosion of OraDisc, and a slow systemic absorption of amlexanox from the drug product.

2.2.5.4 What are the characteristics of drug distribution?

Drug distribution characteristics are included in NDA 20-511 for amlexanox oral paste, no new information has been submitted for the current mucoadhesive dosage form. The drug distribution characteristics of the patch formulation are expected to be comparable to those in oral paste.

2.2.5.5 Does the mass balance study suggest renal or hepatic as the major route of elimination?

No mass balance study was conducted for this application.
The basic pharmacokinetic characteristics of amlexanox were determined in the studies with amlexanox tablets marketed in Japan since 1987. Results of PK studies with amlexanox tablets were considered during the review and approval of the 5% amlexanox paste (NDA20-511, Report No. AA-673/X-108). Serum and urine levels of amlexanox, its M-1 metabolite and conjugates were measured following 12.5, 25, 50 and 100 mg tablets. The urinary excretion of M-1 metabolite was similar for all doses, ranging from 5.3 to 9.7%. Studies done with amlexanox paste 5% showed that a single dose of 100 mg of paste (a dose considered approximately equivalent to 2 mg patch), a total of 17%± 12% was recovered in the urine. Amlexanox and its conjugates accounted for 7.8% of the dose, the metabolite M-1 accounted for 6.25% of the dose, and an additional 3% of the dose was conjugates of M-1.

2.2.5.6 What are the characteristics of drug metabolism?

The basic pharmacokinetic characteristics of amlexanox were determined in the studies with amlexanox tablets marked in Japan since 1987. Systemically absorbed amlexanox is metabolized by hydroxylation to form the M-1 metabolite and some unidentified conjugates. M-1 metabolite concentrations in serum were approximately 10% of the serum amlexanox concentrations.

2.2.5.7 What are the characteristics of drug excretion?

Based on NDA 20-511 for amlexanox oral paste, no new information has been submitted for the current mucoadhesive dosage form.
Please also see the above Section 2.2.5.5

2.2.5.8 Based on pharmacokinetic parameters, what is the degree of linearity in the dose-concentration relationship?

Due to smaller sampling size, with two patch (N=1, Study No. AP-C-1U107, and N=5 Study No. AP-C-1U106) and three patch (N=3, Study No. AP-C-1U107 and N=2, Study No. AP-C-1U106) treatments with OraDisc, no conclusive results on the systemic availability can be inferred.

However, the mean Cmax values tended to increase with increasing number of OraDisc applied with a statistically significant difference ($p = 0.027$, two sample t-test) when comparing the Cmax values for one and three OraDiscs in the Phase I Study No. AP-C-1U107.

2.2.5.9 How do the pharmacokinetic parameters change with time following chronic dosing?

Not applicable.

2.2.5.10 What is the inter- and intra-subject variability of pharmacokinetic parameters in volunteers and patients, and what are the major causes of variability?

As indicated in the PK results, there is a substantial inter-subject variability in the Cmax and AUC0-24 values presumably due to individual variation in the amount and rate of systemic absorption.

2.3. Intrinsic Factors
Other than inclusion of adolescent subjects in the Phase 3 trial AP-C-U106 no additional information that will allow assessment of intrinsic factors has been submitted.

2.4. Extrinsic factors
On August 13, 2004, the Sponsor submitted a 4-month safety update report (project no. 104341) on the potential of amlexanox to inhibit the activity of various CYP450 isozymes. Based on the results of this report, the effects of 10 uM amlexanox on CYP450 1A2, 2C19, 2D6 and 3A4 were less than 10% inhibition or stimulation. In the pivotal clinical trial, the maximum concentration of amlexanox was less than 400 ng/ml or 1.3 uM. There were no appreciable effects of amlexanox at 0.1 or 1 uM concentration on CYP 450 2C9 isozyme. Thus, amlexanox is unlikely to have an effect on drugs or xenobiotics metabolized by CYP450 1A2, 2C9, 2C19, 2D6 and 3A4.

2.5 General Biopharmaceutics

2.5.1 Based on biopharmaceutics classification system (BCS) principles, in what class is this drug and formulation? What solubility and permeability data support this classification?

The applicant has not provided any permeability data. As noted above under physical properties, amlexanox is insoluble in water.

2.5.2. What is composition of the to-be-marketed formulation?

Each patch contains 2 mg of amlexanox as part of a multi-layer patch consisting of ethylcellulose, FD&C Blue #1, FD&C Red #40, hydroxyethylcellulose, hypromellose, methylparaben, modified starch, polycarbophil, povidone, propylene glycol, propylene glycol monostearate, purified water, sodium benzoate, sodium carboxymethylcellulose

2.5.3 What is the in vivo relationship of the proposed to-be-marketed formulation to the pivotal clinical trial formulation in terms of comparative exposure?

The proposed formulation for the to-be-marketed oral patch is same as the formulation used in the pivotal clinical studies.

2.5.4 What moieties should be assessed in bioequivalence studies?

No BE studies were done. For the PK measures in bioavailability studies, the active moiety amlexanox was assessed.

2.5.5 What is the effect of food on the bioavailability of the drug from the dosage form? What dosing recommendation should be made, if any, regarding administration of the product in relation to meals or meal types?

Not applicable to the drug product as OraDisc is to be used topically.

2.5.7 Has the applicant developed an appropriate dissolution method and specification that will assure in vivo performance and quality of the product?

Yes., the applicant has conducted dissolution testing using the following method.

Apparatus: USP Apparatus 2,
Rotation: [ ] rpm
Medium: Artificial Saliva* Volume 900 mL
Specification: NLT [ ] of the active ingredient released within 60 minutes.
*Composition of the artificial saliva: [

]

The dissolution results are provided in the Table below:
In Vitro Dissolution with New Formulations

Study No.	Batch No.	No. of Units	Mean %±SD Dissolved (Range)			
			15 min	30 min	45 min	60 min
AP 03-10-01	BMS 4259	N=6	[			]
			[			]

The dissolution study was conducted using the patches from Batch BMS-4259 that was also used in phase 3 clinical trial study.

The product was designed to erode in the mouth after approximately one hour. The data from Study AP-C-1U107 show that it took an average of [ ] minutes for half the OraDisc patch to erode. By an average of [ ] minutes most of the patch had eroded. Based on the dissolution results, the firm justifies that the proposed specification of NLT [ ] active release within 60 min is a reasonable measure of the ability of the patch to deliver the majority of the active components within the residence time of the patch in the mouth.

As reported by the Sponsor (Section 3.2.P.2.8), the % release of the OraDisc 2 mg patch (N=6) are [ ] (range [ ]) and [ ], [ ], at [ ] and 60 minutes, respectively. The Agency requests the Sponsor to set an interim dissolution specification of NLT(Q) [ ], at 60 minutes.

2.6 Analytical Section

2.6.1 Were relevant metabolite concentration measured in the clinical pharmacology and biopharmaceutics studies?

The applicant measured the active moiety amlexanox in serum samples in all pharmacokinetic studies included in this submission. Urinary data were submitted in the data from oral paste and tablet formulation submissions and no urinary metabolites in the studies in this submission were measured.

2.6.2 For all moieties measured, was free, bound, or total measured? What is the basis of that decision, and is it appropriate?

- Total amlexanox concentrations in serum were measured.

2.6.3 Were the analytical procedures used to determine drug concentration in this NDA acceptable?

Yes. Amlexanox was quantified in serum by means of a validated HPLC assay using UV detection. The limit of detection (LOQ) was [ ] ng/mL. Calibration standards employed drug concentrations from [ ] ng/mL with a correlation coefficient of 0.9996. Intra- and inter-run accuracy ranged [ ] respectively. The intra- and inter-run precision were [ ] respectively. The long term frozen stability in human serum at -20° C for up to12 months and freeze thaw stability for [ ] were acceptable. The applicant has provided adequate documentation of method validation and in-study validation.

3. Detailed Labeling Recommendations

[

]

7 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

4.2. Clinical Pharmacology and Biopharmaceutics Individual Study Review

1. Phase 1 Study with the Final Formulation Single Dose.
Protocol AP-C-1U107: A phase I study to investigate the pharmacokinetic characteristics of Amlexanox OraDisc 2 mg, in 18 subjects with minor Aphthous ulcers after a single application to 1-3 aphthous ulcers.

Study Design: This was a Phase I, single-center, open-label, single-group, in male and female at least 18 years of age in general good health and presenting with at least one minor aphthous ulcer.
Objectives: Primary: To investigate the pharmacokinetics and safety of amlexanox OraDisc, 2 mg, following a single oral application of 1 to 3 mucoadhesive patches in subjects with minor aphthous ulcers.
Secondary: To collect information on the retention and resorption properties of OraDisc when applied to aphthous ulcers.

Study Center: [redacted]
Investigator:
Analytical Center: [redacted]

Study Subjects: Eighteen subjects (10 females and 8 males) at least 18 years of age in general good health and presenting with at least one minor aphthous ulcer were included in the study. All 18 subjects completed the study. The number of ulcers at baseline varied from 1 to 4 with most subject (14) having only one ulcer. Baseline oral status, number of ulcers and size of ulcers at study entry are described in detail in Module 1.5, Vol. 1.2, Sec. 5.3.2.2, pp. 32.

The mean and range for age, weight and height were 36 years (range 18-63), 76 kg (range 54-98) and 174 cm (range 160-191), respectively. There were 11 Caucasian (5 males and 6 females) and 7 Black (2 males and 5 females). Inclusion and exclusion criteria are described Module 5, Vol. 1.2, Sec5.3.3.2, pp. 16-17.
Dosage and Administration: Each subject applied one mucoadhesive patch to each ulcer up to a maximum of 3 patches. Disposition of subjects entered into study was as follow:

	Male	Female	1 Patch	2 Patches	3 Patches
No. of subjects enrolled	8	10	14	1	3
No. of subjects completed the study	8	10	14	1	3

Study Dates: Clinical study was performed between July 2, 2002 to January 11, 2003
Analytical: Samples were analyzed between Feb 26, 2003 to March 05, 2003.
Drug Formulations: Test: Amlexanox OraDisc: Lot No. BMS 4257/CSI 10594.
Criteria for Evaluation:
Pharmacokinetics: Serum samples 7.0 mL pre-dose (0) and at 0.5, 1, 2, 3, 4, 6, 8, 10, 12 and 24 hours post-dose after application of the adhesive mucosa.
Retention, Resorption: On Day 1 at 0. 5. 15, 30, 45, 60, 75, 90 and 120 minutes after application of the mucoadhesive patch, an evaluator recorded the levels of:

- retention on a 6-point scale of 0-5, and
- resorption (solid particle free in the oral cavity at any time: yes/no).

Analytical Determinations:

Amlexanox was quantified in serum by means of a validated HPLC assay using UV detection. The limit of detection (LOQ) was [ ] ng/mL. Calibration standards employed drug concentrations from [ ] ng/mL with a correlation coefficient of 0.9996. Intra- and inter-run accuracy ranged [ ] respectively. The intra- and inter-run precision were [ ] respectively. The long term frozen stability in human serum at -20 C for up to 6 months and freeze thaw stability for [ ] were acceptable. The mean accuracy for the 5- and 20-fold diluted samples were within ±15%. No interference was noted with regards to selectivity and specificity. The analytical validation is described in detail in Module 5, Vol. 1.2, 1.6, and 1.7.

Results:

Patch Retention and Resorption Scores:

Summary statistics for patch retention scores are presented in the following Table and Figure. A score of 3 and 2 meant that the patch has eroded to 75-50% and 50-25% of its original surface area, respectively.

Mean (S.D.) Patch Retention Score* over Time

Time after Patch Application (minutes)	Mean (S.D.) Retention Score		
	All (N=18 subjects, 25 patches)	Female (N=10 subjects, 15 patches	Male (N=8 subjects, 10 patches)
0	5.0 (0.0)	5.0 (0.0)	5.0 (0.0)
5	5.0 (0.0)	5.0 (0.0)	5.0 (0.0)
15	4.6 (1.8)	4.6 (0.5)	4.7 (0.5)
30	3.3 (1.8)	3.2 (1.7)	3.5 (1.9)
45	2.6 (1.7)	2.5 (1.5)	2.6 (2.0)
60	1.8 (1.6)	1.9 (1.5)	1.7 (1.9)
75	1.2 (1.1)	1.4 (1.0)	0.9 (1.3)
90	0.8 (1.0)	0.7 (1.0)	0.8 (1.1)
120	0.2 (0.5)	0.2 (0.4)	0.2 (0.6)

**Retention scale*:*

5 Complete patch
4 Almost complete patch (<100% to 75% of original size)
3 Gelatinous mass (75% to 50% of original size)
2 Gelatinous mass (50% to 25% of original size)
1 Gelatinous residue or debris
0 No observable material/residue

In 3 subjects, the patch was dislodged between 15 to 30 minutes after application. Subjects 13 and 18 reported the patch adherence to the teeth and Subject 17 the patch dislodged while the subject was blowing his nose. The study evaluator could not confirm whether the loose patches were swallowed or expelled after they were dislodged.

Based on the interpolation of the data, it took an average of 47 minutes to erode half of the patch and 82.5 min to erode all of the patch.

Based on results of statistics for patch resorption (presence or absence of loose particles in the oral cavity) a majority of subjects (12/18, 66.7%) reported feeling some type of debris during the 2 hours of observation.

Pharmacokinetic Results:
Mean and individual serum PK parameters are presented in Tables 3 and 4, and serum-amlexanox concentration profile is depicted in Figure 1 below. The values for Cmax and AUC0-24 were normalized for dose and body surface area. The highest observed serum concentration of amlexanox for a subject who received one patch was [ ] ng/mL, and the lowest measurable Cmax was [ ] ng/mL. The mean concentration was 45.4 ± 39.6 (range [ ] ng/mL, N=14).

Of the 14 subjects who received one OraDisc, one subject (#13) did not have measurable concentration of amlexanox at any sampling time, and 4 subjects (#8, 14, 17 and 18) had concentrations of 10 ng/mL or less at all sampling times. The mean Cmax and AUC0-24 of amlexanox in 13 subjects with measurable levels, were 45.4 ng/mL (range [ ] and 258 ng.hr/mL (range [ ], respectively.

The Cmax value for the subject who received 2 OraDisc was 138 ng/mL 3-hr post-dose. However, no statistical inference could be made due to limited number of subject (N=1). As indicated in the results Table 3 below, there is a substantial inter-subject variability in the Cmax values presumably due to individual variation in the amount and rate of systemic abruption. However, the mean Cmax values tended to increase with increasing number of OraDisc applied with a statistically significant difference ($p = 0.027$, two sample t-test) when comparing the Cmax values for one and three OraDiscs.

Tmax occurred at approximately 3 hr (mean Tmax of 2.8±1.7, 3.0 and 3.0±1.0 hr for one, two and three OraDisc, respectively). Most subjects observed a lag time (T_{lag}) of 0-0.5 hours. A Tlag of 0-1 hour was observed in 9/13 (69%) of the subjects receiving one OraDisc treatment. The mean half-life values were 4.5 ± 2.0 and 8.8 ± 3.5 for subjects who received one or three patches, respectively, the half-life for the one subject who received two patches was 3.2 hr. The Tmax and Tlag were very similar in both genders with no statistical difference ($p > 0.3$ for both parameters). There were no significant differences in the values of Ke and t1/2 also ($p \geq 0.5$).

The mean values for AUC_{0-24} for one and three OraDiscs were 258 ± 238 and 605 ±356 ng·hr/mL, respectively.

Table 3. . Mean Pharmacokinetic Parameters Phase 1 Study AP-C-1U107

Parameter	One Patch 2 mg	Two Patches 4 mg	Three Patches 6 mg	Male (All doses)	Female (All doses)
Cmax (ng/mL) Mean ±SD Median (range)	N=14 45.4±39.6 39.8 [ ]	N=1 138	N=3 168.3±191.5 79.9 [ ]	-	-
Tmax (hr) Mean ±SD	N=13 2.8±1.7	N=1 3	N=3 3.0±1.0	N=8 2.5±0.9	N=9 3.1±1.9

Median (range)	2 (1-8)		3 (2-4)	2.5 (1-4)	3 (2-8)
T_{lag} (hr)	N=13	N=1	N=3	N=8	N=9
Mean ±SD	1.0±0.6	1	1.0±0.9	1.1±0.6	0.8±0.5
Median (range)	1 [ ]		0.5 [ ]	1.0 [ ]	0.5 [ ]
AUC_{0-24} (ng·hr/mL)	N=14	N=1	N=3		
Mean ±SD	258±238	475	605±356	-	-
Median (range)	226 [ ]		584 [ ]		
$T_{1/2}$ (hr)	N=7	N=1	N=3	N=4	N=7
Mean ±SD	4.5±2.0	3.2	8.8±3.5	4.7±2.3	6.1±3.4
Median (range)	4.5 [ ]		10.3 [ ]	4.1 [ ]	5.0 [ ]

Table 4 Individual Pharmacokinetic Measures for Single Dose Phase Study No.AP-C-1U107

Table 12-5: Non-compartmental Pharmacokinetic Parameters by Subject

Pat. I.d.	Age, Sex	Weight (kg)	Height (cm)	BSA (m^2)	Dose (mg/m^2)	Cmax (ng/mL)	Normalized Cmax (ng/mL)/(mg/m^2)	T_{max} (hour)	T_{lag} (hour)	AUC_{0-24} (ng·hr/mL)	Normalized AUC_{0-24} (ng·hr/mL)/(mg/m^2)	r^2	k_e (hr^{-1})	$t_{1/2}$ (hour)	$AUC_{(0-\infty)}$ (ng·hr/mL)
ONE PATCH															
01	24, F	53.7	170	1.62	1.24										
02	24, M	86.6	186	2.11	0.95										
03	24, F	70.9	178	1.88	1.06										
05	40, M	76.2	174	1.91	1.05										
07	60, F	71.6	169	1.82	1.10										
08	31, M	89.5	191	2.19	0.91										
11	28, M	73.7	185	1.97	1.02										
12	53, F	65.8	172	1.78	1.13										
13	26, F	86.6	168	1.96	1.02										
14	42, M	98.0	181	2.19	0.92										
15	32, F	58.2	160	1.60	1.25										
16	27, F	84.1	171	1.96	1.02										
17	18, M	71.4	178	1.89	1.06										
18	37, M	81.4	171	1.94	1.03										
TWO PATCHES															
09	53, F	74.6	161	1.79	2.24										
THREE PATCHES															
04	24, F	61.4	170	1.71	3.51										
06	48, F	69.9	176	1.85	3.24										
10	63, M	94.5	179	2.13	2.81										

* *Numbers in italics are considered questionable due to very poor fit of data to regression line for half-life (r^2 < 0.90)*
** *NC = not calculated*
Source: Data Listing 16.2.8 and Pharmacokinetic Methods Appendix 16.1.6.

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Figure 1 Mean Plasma Amlexanox Concentration-Time Plot: Phase I Study AP-C-107

Figure 12-3: Linear Plot of Mean Serum Concentrations of Amlexanox by Dose Group

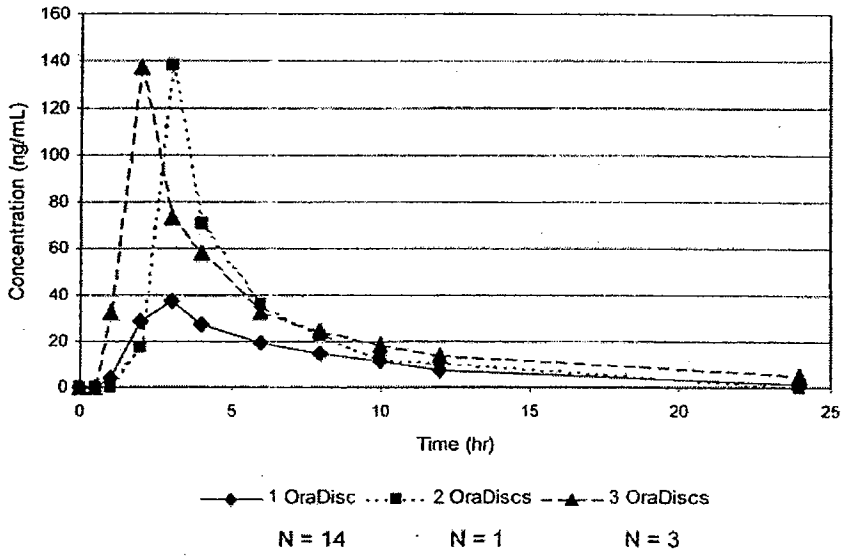
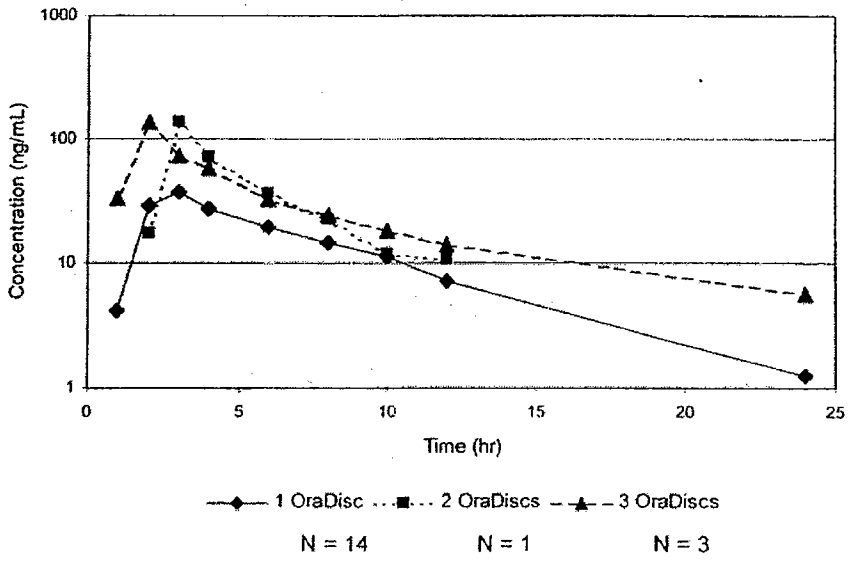


Figure 12-4: Semilog Plot of Mean Serum Concentrations of Amlexanox by Dose Group



Comments
Based on the reported Tlag (0-1 hr) and mean Tmax (~ 3 hours), there appears to be no or little absorption of amlexanox rapidly and directly through the aphthous ulcers. The lag time and Tmax values indicate a slow erosion of OraDisc, and a slow systemic absorption of amlexanox from the drug product.

Considering the AUC data from the one and three OraDisc treatment, there is a no trend of nonlinearity over the range of 2 to 6 mg dose, however, the number of subjects (N=3) in the 6 mg dose (i.e., 3 OraDisc) is too small to reach any conclusion on the dose proportionality.

With regards to effect of gender on the pharmacokinetic of OraDisc, there appears to be more absorption of amlexanox in females than in males. However, there appears to be no gender effect on the rate of elimination of amlexanox from the OraDisc treatment.

2. Phase 3 Study with New Formulation Multiple Dose.
Protocol AP-C-1U106: A phase 3 evaluator-blinded, randomized, parallel-group study to determine the effects the Amlexanox Mucoadhesive patch, OraDisc 2 mg on the healing of recurrent minor aphthous ulcers as compared with vehicle Mucoadhesive patches or no treatment.

Study Design: This was a Phase 3, multi-center, multi-dose, evaluator-blinded, parallel-group, vehicle-controlled, no-treatment-controlled, parallel-group study in male or females at least 12 years of age in general good health and with a reported history of recurrent minor aphthous ulcers taking 5 days or more to resolve, patients were to have at least one identifiable ulcer of the oral mucosa that has developed within 36 hours prior to enrollment. Patients were randomized to 3:3:1 to active patches, vehicle patches or no-treatment. The "no-treatment' arm was included in order to demonstrate that the vehicle patch did not have a worsening, irritating effect on the aphthous ulcers.

Objectives:
- To determine the effect of amlexanox formulated as OraDisc on the healing rate of recurrent aphthous ulcers patients presenting with recurrent minor aphthous ulcers9s).
- To evaluate the safety of amlexanox OraDisc by determining the frequency of treatment-emergent adverse events.
- To measure serum levels of amlexanox after multiple applications of OraDisc.

Secondary: To collect information on the retention and resorption properties of OraDisc when applied to aphthous ulcers.

Study Center: Twenty-six study centers in the US.
Analytical Center: [redacted]

Study Subjects: Seven hundred and one patients at least 12 years of age in general good health and with a reported history of recurrent minor aphthous ulcers taking 5 days or more to resolve, patients were to have at least one identifiable ulcer of the oral mucosa that has developed within 36 hours prior to enrollment.

Of the 701 patients randomized, 458 were women (65%) and 243 (35%) were men. Ages ranged from 12 to 75 with a mean age of 29.3 years and a median of 26. A majority of patients were Caucasians 601(86%), 54 were Hispanic (8%), 14 (2%) were Asian and 15 (2%) were African American, and 17 (2%) were of mixed race. Details of demographic characteristics are reported in Module 5, Vol 1.3, Sec 5.3.5.1, pp 54.

Disposition of patients entered into study is as follow:

		OraDisc	Vehicle	No Treatment	Overall
No. of patients randomized		303	301	97	701
By Age Group	12-14 yrs	15	27	7	49
	15-17 yrs	22	22	5	49
	18-64 yrs	263	248	84	595
	≥ 65 yrs	3	4	1	8
No. of patients completed the study		284	290	89	663
	12-17 yrs	36	49	12	97
	≥ 18 yrs	248	241	77	566
No. of patients withdrew from the study		19	11	8	38
	12-17 yrs	1	0	0	1
	≥ 18 yrs	18	11	8	37
Reasons for withdrawal					
Worsening of condition		2	0	0	2
Adverse Events		0	4	0	4
Patients request		8	2	7	17
Protocol violation		3	2	0	5
Lost to follow up		4	1	1	6
Other reason		2	2	0	4

Dosage and Administration: Patches were applied four times a day (after each meal and at bed time) directly over the designated ulcer(s) for 7 days or until all treated ulcers healed, whichever occurred first. Up to maximum of 3 ulcers were treated per patient.
Dosage: (1) Amlexanox patch containing 2 mg of amlexanox, (2) Vehicle patch, or (3) No treatment.
Duration of patient participation: 7 days or until all treated ulcers healed, whichever occurred first.

Drug Formulations:	Lot Numbers.:	Amlexanox OraDisc	Vehicle
		BMS-4257	BMS-4254
		BMS-4258	BMS-4255
		BMS-4259	BMS-4256

Inclusion and Exclusion Criteria are provided on page 27-28, Module 5, Vol 1.3.
Rationale for Dose Selection and Dosage Regimen: The 2 mg amount of amlexanox in each OraDisc corresponds to the average amount of amlexanox in one dab of amlexanox paste, 5%, which is currently marketed in the United States. The frequency of 4 times per day is also identical to the frequency that was proved efficacious for the amlexanox paste.

Study Dates: Clinical study was performed between June 3, 2002 to March 23, 2003
Analytical: Samples were analyzed between April 07, 2003 6 and April 18, 2003.
Analytical Determinations:
Amlexanox was quantified in serum by means of a validated HPLC assay using UV detection by [ ] as described above for study AP-C-1U107.

Pharmacokinetic Criteria for Evaluation:
Pharmacokinetics: The blood samples were collected on Day 4 at the following time points to estimate the trough and peak levels:
Prior to the first patch application, and two hours after the first patch application. A total of 152 samples were collected from 77 patients at 7 study centers (for details please see pages 36-37, and page 81-82. Module 5, Vol. 1.3). Of these samples, 60 were obtained from 31 patients in the Amlexanox OraDisc group. All but 2 provided both pre-dose and 2-hour post-dose samples. Sixty-six samples were obtained from 33 patients and 26 samples were obtained from 13 patients from the vehicle patch and no treatment groups, respectively. Of the 31 patients treated with OraDisc only 3 were in the age range of 12 to 18 years.
Pharmacokinetic results: Mean and individual serum concentrations from the patch treatment group are presented in Tables 5 and 6 below. No amlexanox was detected in any of the samples taken from patients in the vehicle and no treatment groups reported at the LOQ level of [ ] ng/mL. The PK results obtained from the OraDisc-treated group is summarized in the Table below:

Table 5. Mean Pharmacokinetic Parameters for the Patch Treatment Group Phase 3 Study AP-C-1U106

Treatments	Amlexanox Serum Concentrations (ng/mL)	
	Prior to First Dose on Day 4	Two hours after First Dose on Day 4
All Patients		
Mean SD	16.0 ±31.7 (N=31)	20.9 ±24.1 (N=29)
Median (Range)	6.6 [ ]	14.8 [ ]
Pediatric Patients (N=3)		
	3.7± 5.2 [ ]	13.5±12.3 [ ]
Patients Treated with One Patch, 4x daily		
Mean SD	9.8±16.5 (24)	15.8±16.4 (N=24)
Median (Range)	5.6 [ ]	11.5 [ ]
Patients Treated with Two Patches, 4x daily		
Mean SD	43.9±68.5 (N=5)	44.4±42.7 (N=5)
Median (Range)	10.0 [ ]	35.4 [ ]
Patients Treated with Three Patches, 4x daily		
Mean SD	20.4 (N=2)	18.6 (N=2)
Median (Range)	20.4 [ ]	18.6 [ ]

Table 6. Individual Serum Concentrations Patch Treatment Group Phase 3 Study AP-C-1U106

Patient ID	Pre Dose	2-hr post dose
One Patch		
057	[redacted]	[redacted]
099		
100		
109		
141		
150		
151		
187		
261		
262		
263		
276		
277		
291		
327		
409		
657		
694		
697		
699		
719		
724		
277		
Two Patches		
063		
144		
335		
618		
619		
Three Patches		
058		
108	[redacted]	[redacted]

BQL=Below quantitation limit, ND=Not detected

Comments:

Prior to first dose on Day 4, the maximum pre-dose concentrations (Cmin) were [redacted] and [redacted] ng/mL for subjects who applied 1, 2 and 3 patches, respectively. The corresponding maximum 2-hr concentrations after first dose on Day 4 concentrations were [redacted] ng/mL. The inter-subject variability was high in all groups. Furthermore, because of low number of subjects in the 2 and 3 patch-treatment group, a dose-dependency could not be established.

The maximum systemic exposure to amlexanox for subjects (N=24) receiving one patch of OraDisc 4 time daily for 3 days was 79 ng/mL. The reported Cmax value for the approved amlexanox product 5% paste is 116 ±71.2 ng/mL (please see Table below).

Due to smaller sampling size, with two patch (N=5) and three (N=2) patch treatments with OraDisc, no conclusive observation on the systemic observation could be inferred.

In study no. BD34,787-110 submitted as part of the NDA 20-511 for the approved Aphthasol 5% oral paste, the following PK characteristics have been reported (N=12, adult population) .

Parameter	Adult Mean ±SD (N=12)
Auc_{0-8} (ng·h/mL)	423.2 ±261.0
Auc_{0-inf} (ng·h/mL)	615.0 ±345.9
Cmax (ng/mL)	116 ±71.2
Tmax (hr)	2.55 ±0.82
Ke	0.215± 0.111
t1/2	3.98± 1.84

Adverse Events in Patients:: There were 96 reports of untoward application site reactions reported by 82 patients, 38 patients in the amlexanox patch group (12.5%) and 44 patients in the vehicle group (14.6%). All application-site events but 3 were deemed potentially related to application of the patches. Pain (reported by 51 patients) and burning (reported by 17 patients) were the most frequent and were reported with similar frequencies in the amlexanox patch and vehicle patch groups. Detail description of the AEs are provided in Tables 13-4, 13.5 and 13-6, page 77, Section 5.3.5.1, Vol 3 of this NDA submission).

Adverse Events in Pediatric Patients: Five patients in the amlexanox (13.5%) and 5 (10.2%) in the vehicle patch groups exhibited untoward application site reactions. All application-site reactions were deemed potentially related to application of the patches and rated as mild. Pain (3 patients) and paresthesia (4 patients) were the most frequent AEs. Eleven pediatric patients reported 14 AEs other than application site reactions. No type or events appeared to be more frequent in the amlexanox group than in the vehicle group.

Study No. AP-C-9E03: A phase 2/3 investigator-blind, randomized, parallel-group study to determine the effects and serum levels of amlexanox disc 2 mg on the healing of recurrent aphthous ulcers as compared with vehicle discs or no treatment in patients 12 years of age or older. In this study the Early Formulation patch was applied qid for 7 days. Serum levels of amlexanox was determined after 3 dull days of treatment before the first application and 1 hour post-dosing on Day 4. The results of this study are summarized in the Table below. As agreed upon between the Sponsor and Agency, the above study AP-C-9E03 is not being considered for approval of this NDA. The PK results from this study have been summarized in the QBR section 2.1 for supportive purpose only.

Sampling Time	Mean ±SD	Median	Range	N
Pre-dose (ng/mL)	54.1 57.0	46.3	[redacted]	19
1 hr post-dose	60.1 64.0	41.2	[redacted]	36

After multiple dosing for at least 3 days, most subjects have low serum levels of amlexanox pre-dose. The serum levels at 1-hr post-dose were similar to the pre-dose levels, suggesting slow absorption probably through the gastrointestinal tract rather than mostly through the oral mucosa of aphthous ulcer.

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4.3 Cover Sheet and OCPB Filing Review Form

Office of Clinical Pharmacology and Biopharmaceutics ***New Drug Application Filing and Review Form***			
General Information about the Submission			
	Information		Information
NDA Number	21-727	Brand Name	OraDisc™A
OCPB Division	DPE III, HFD 880	Generic Name	Amlexanox 2mg, Mucoadhesive Patch
Medical Division	ODE V, HFD 540	Drug Class	Topical
OCPB Reviewer	Chandra S. Chaurasia, Ph. D.	Indication(s)	Treatment [[of aphthous ulcers in adults and adolescents 12 years of age or older (as proposed by the Sponsor).
OCPB Team Leader	E. Dennis Bashaw, Pharm. D.	Dosage Form	Mucoadhesive Patch
Type of Submission	Original Submission	Strength	2 mg
Related NDAs/ANDAs/INDs	IND 59,949	Route of Administration	Topical administration to the oral mucosa
Date of Submission	Dec 09, 2003	Dosing Regimen	Four times daily after breakfast, lunch, dinner and [ ] before bedtime. In case of multiple ulcers, apply one patch to each ulcer.
Estimated Due Date of OCPB Review	Jun 09, 2004	Sponsor	Access Pharmaceuticals, Inc. Dallas, TX 75207-2107
PDUFA Due Date	Oct 08, 2004	Priority Classification	
Division Due Date			

Clin. Pharm. and Biopharm. Information				
	"X" if included at filing	**Number of studies submitted**	**Number of studies reviewed**	**Critical Comments If any**
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	*X*			
Labeling				

Reference Bioanalytical and Analytical Methods	X			HPLC, LLOQ [ ] ng/mL, Range [ ] ng/mL [ ]
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose in **pediatric population**:	X			**1. Study with Aphthasol Oral Paste 5%. Single Dose.** **Study No. BD98-006:** A phase 1 open label study in children to determine the pharmacokinetics of amlexanox after a single topical administration of 5 amlexanox paste % to the oral mucous membrane. N=12 healthy (6 males and 6 females) age 8-12 years, 105 to 120 mg of amlexanox of 5% paste. Serum Samples collected at pre-dose, 0.5, 1, 2, 3, 4, 6 and 8 hours post-dose. Urine Samples collected at pre-dose, 0-6 hr, 6-12 hr and 12-24 hr. Determined with HPLC **with LOQ [ ] ng/mL.**
multiple dose:				

Patients-					
single dose:				**1. Study with New Formulation Single Dose.** **Protocol AP-C-1U107:** A phase I study to investigate the pharmacokinetic characteristics of Amlexanox OraDisc 2 mg, in 18 subjects with minor Aphthous ulcers after a **single** application to 1-3 aphthous ulcers. N=18 (8 males, 10 females), age 18-63 (mean 36) Criteria for Evaluation: Retention on Day 1, at 0, 5, 15, 30, 45, 60, 75, 90 and 120 minutes after application Resorption: solid particle free in the oral cavity at any time yes/no Pharmacokinetics: Cmax, AUC0-24 and Tmax, also normalized for dose and body surface area:		
multiple dose:					
Dose proportionality -					
fasting / non-fasting single dose:					
fasting / non-fasting multiple dose:					
Drug-drug interaction studies -					
In-vivo effects on primary drug:					
In-vivo effects of primary drug:					
In-vitro:					
Subpopulation studies -					
ethnicity:					
gender:	*X*				Pooled Data
pediatrics:		**X**			
geriatrics:					
renal impairment:					
hepatic impairment:					
PD:					
Phase 2:					
Phase 3:					
PK/PD:					
Phase 1 and/or 2, proof of concept:					

Phase 3				**1. Study with New Formulation, Multiple Dose:** **Protocol AP-C-1U106**: A phase 3 evaluator-blinded, randomized, parallel-group study to determine the effects the Amlexanox Mucoadhesive patch, OraDisc 2 mg on the healing of recurrent minor aphthous ulcers as compared with vehicle Mucoadhesive patches or no treatment. N=77 (for PK) at 7 clinical centers with 31 treated with OraDisc A patch. Treatment continues for 7 days or until all ulcers present at baseline healed. On day 4 of dosing, serum was collected before the first application and 2 hours after application. **2. Study with Early Formulation** **Protocol AP-C-9E03**: A phase 2/3 investigator-blinded, randomized, parallel-group study to determine the effects of Amlexanox disc, 2 mg on the healing of recurrent aphthous ulcers as compared with vehicle or no treatment. PK objective to determine the serum levels of amlexanox after 3 full days of treatment with Early formulation N=137 (for PK) at 5 clinical centers. Treatment continues for 7 days or until all ulcers present at baseline healed, whichever occurred first. On day 4 of dosing, serum was collected before the first application and 1 hours after application.

Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution: In Vitro	**X**			**1. Study AP 03-10-01** to compare dissolution profile and delivery characteristics of Early Formulation and Final Formulation.

(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References	X			
Total Number of Studies		5		

Filability and QBR comments		
	"X" if yes	Comments
Application filable?	YES	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
QBR questions (key issues to be considered)	• What are the properties of the formulation of the drug product? • What are the differences between Early Formulation (used in Phase I trials) and Final Formulation (used in Phase 3 trials)? • Are the dissolution profile of the Early and Final Formulation Comparables? • Are the active moieties in the serum appropriately identified and measured to assess pharmacokinetic parameters? • Are analytical methods sensitive enough to determine the extent of amlexanox absorption after topical buccal administration? • Can any meaningful result obtained from the pediatric pharmacokinetic study using Amlexanox 5% Oral Paste? • Is there a significant systemic absorption of amlexanox from the OraDisc 2 mg patch in the adults and adolescent (≥12 yrs of age) in the Phase 3 studies?	
Other comments or information not included above	In addition to the above 4 PK studies (3 with OraDisc and 1 with amlexanox 5% paste in pediatrics), the Sponsor has cited PK results from the approved amlexanox 5% oral paste (NDA 20-511) and amlexanox oral tablets (12.5, 25, 50 and 100 mg, submitted in support of NDA 20-511).	
Primary reviewer Signature and Date	**Chandra S. Chaurasia, Ph. D.**	
Secondary reviewer Signature and Date	**E. Dennis Bashaw, Pharm. D.**	

Chandra S. Chaurasia, Ph.D. _____ Date: _____
Clinical Pharmacology and Biopharm Reviewer
Division of Pharmaceutical Evaluation III

NDA 21-727
Amlexanox 2 mg Patch, DFS Copy

RD/FT Initialed by E. Dennis Bashaw, Pharm.D. _____ Date: _____

CC: NDA 21-727, HFD-850 (P. Lee), HFD-540 (J. Smith), HFD-880 (D. Bashaw, J. Lazor, A. Selen)

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Chandra S. Chaurasia
9/2/04 09:48:56 AM
BIOPHARMACEUTICS

Arzu Selen
9/2/04 11:02:35 AM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 21-727

Administrative/Correspondence Reviews

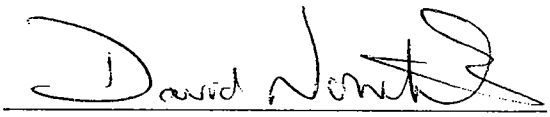
1.3.1 Patent Information

Access Pharmaceuticals, Inc., holds the following patents issued by the U.S. Patent and Trademark Office:

U.S. Patent No. 6,585,997; Moro et al. Mucoadhesive erodible drug delivery device for controlled administration of pharmaceuticals and other active compounds. Issued July 1, 2003, Expires August 16, 2021.

U.S. Patent No. 5,362,737; Vora et al. Methods of treating aphthous ulcer and other mucocutaneous disorders with amlexanox. Issued November 8, 1994, Expires July 19, 2013.

The under signed declares that Patent No.'s 6,585,997 and 5,232,637 cover the formulation, composition, and/or method of use of OraDisc™A, Amlexanox 2 mg, Mucoadhesive Patch. This product is the subject of this application for which approval is being sought.



David P. Nowotnik, Ph.D.
Senior Vice-President, Research & Development

EXCLUSIVITY SUMMARY FOR NDA # 21-727_____ SUPPL #_____

Trade Name TRADENAME__ Generic Name amlexanox_____

Applicant Name Access Pharmaceuticals___HFD # 540

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /_X_/ NO /___/

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

_505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X__/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

d) Did the applicant request exclusivity?

YES /_X__/ NO /___/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____3_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X__/

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an

esterified form of the drug) to produce an already approved active moiety.

YES /_X__/ NO /_ __/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _20-511 Aphthasol® 5% Oral Paste

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

N/A YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered ``NO'' for original approvals of new molecular entities.) IF ``YES'' GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations

(other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /_X__/ NO /_ __/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X__/

If yes, explain:

---

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /__X_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

AP-C-1U106 (Pivotal); AP-C-9E03 (Supportive)

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a

previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /_X__/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /_X__/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Study AP-C-1U106 (Pivotal) _____

Study AP-C-9E03 Supportive) _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
Study AP-C-1U106

IND # 59,949 YES /_X__/ ! NO /___/ Explain: _____

Investigation #2
Study AP-C-9E03 (Supportive)

IND # _59,949____ YES /__X_/ ! NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X__/

If yes, explain: _____

_____

Signature
Title:

Date

Signature of Office/
Division Director

Date

Form OGD-011347 Revised 05/10/2004

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-610/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-727 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

HFD-540 **Trade and generic names/dosage form:** OraDisc™ A (Amelexanox 2mg, Mucoadhesive Patch)

Applicant: Access Pharmaceuticals, Inc. **Therapeutic Class:** 3S

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Treatment of Aphthous Ulcers

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**

- X **No: Please check all that apply:** X **Partial Waiver** **Deferred** ___ **Completed** X
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min	**kg**	**mo.** 0	**yr** 0	**Tanner Stage**	
Max	**kg**	**mo.** 0	**yr.** 12	**Tanner Stage**	

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- X **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:** Impractical to use under age 12.

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
  There are safety concerns
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:
Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr. 12 Tanner Stage_____
Max_____ kg_____ mo._____ yr. 17 Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Jacquelyn Smith, M.A.
Regulatory Project Manager

cc: NDA
HFD-960/Grace Carmouze
(revised 12-22-03)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

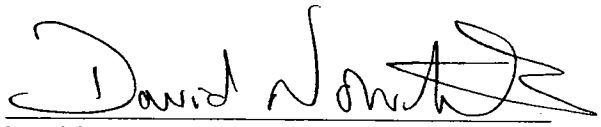
Fred Hyman
2/9/04 10:08:09 AM
Fred Hyman is Acting Division Director today for Jonathan Wilkin

1.3.8 Exclusivity Claims

OraDisc™A, Amlexanox 2mg, Mucoadhesive Patch is the subject of this original New Drug Application. The active ingredient, amlexanox, has been previously approved by FDA for use in Aphthasol® (amlexanox oral paste) 5%, the subject of NDA 20-511.

Under IND# 59,949, Access Pharmaceuticals, Inc. has sponsored two safety and/or efficacy clinical trials with OraDisc™A (Study AP-C-1U106 and Study AP-C-2U108) that are "essential to the approval" of this application. Neither of these studies has been relied upon by the Agency to demonstrate the safety or efficacy of Aphthasol® (amlexanox oral paste) 5%. Furthermore, there are no published studies relevant to the safety and efficacy of the OraDisc™A drug product, and the publicly available data will not independently support approval of this New Drug Application.

Access Pharmaceuticals, Inc., hereby requests a three-year new dosage form exclusivity term for OraDisc™A, Amlexanox 2mg, Mucoadhesive Patch as described in 21 CFR 314.108.



David P. Nowotnik, Ph.D.
Senior Vice-President, Research & Development

1.3.2 Debarment Certification

Access Pharmaceuticals, Inc., hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

David P. Nowotnik, Ph.D.
Senior Vice-President, Research & Development

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information			
NDA 21-727	Efficacy Supplement Type SE- N/A	Supplement Number N/A	
Drug: TRADENAME (amlexanox) Mucoadhesive Patch, 2mg		Applicant: Access Pharmaceuticals	
RPM: Jacquelyn Smith		HFD-540	Phone # 301-827-2020
Application Type: (X) 505(b)(1) ( ) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** ( ) Confirmed and/or corrected		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	3S
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Dates	October 8, 2004
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	(X) Paid UF ID number 4675
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify) N/A
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify) N/A
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No

• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	( ) Verified (No FDA-3542a form submitted) Patent Statement was submitted.
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	N/A 21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	N/A
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	( ) N/A (no paragraph IV certification) ( ) Verified N/A
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).* (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (3).* (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	( ) Yes ( ) No N/A ( ) Yes ( ) No N/A ( ) Yes ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*	N/A
(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No,**" continue with question (5).*	( ) Yes ( ) No N/A
(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "**No,**" there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes,**" a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes ( ) No N/A

❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	Exclusivity summary was in application. Please note: This a 505(b)(1) application.
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	N/A

General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	( ) Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	Draft label to sponsor (9/16/04)
• Most recent applicant-proposed labeling	9-24-04
• Original applicant-proposed labeling	12-4-03
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DDMAC(7-15-04); DMETS (8-13-04)
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	Draft label to sponsor (9/16/04)
• Applicant proposed	12-4-03
• Reviews	9-20-04
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	No requests
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	August 20, 2001
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other (Guidance Meeting)	August 13, 2003
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	Med. TL/ 9-24-04
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	9-24-04
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	9-22-04 (from clinical review)
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	2/6/04
❖ Demographic Worksheet *(NME approvals only)*	N/A
❖ Statistical review(s) *(indicate date for each review)*	9/10/04
❖ Biopharmaceutical review(s) *(indicate date for each review)*	9/2/04
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	No DSI inspection
• Bioequivalence studies	No DSI inspection
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	9-24-04
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	9-24-04
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	
❖ Facilities inspection (provide EER report)	Date completed: 9/14/04 (**X**) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed (**X**) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	8/6/04
❖ Nonclinical inspection review summary	No
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	No
❖ CAC/ECAC report	No

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

Appears This Way
On Original

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

Date: September 24, 2004

To: Amy Campbell, Manager, Regulatory Affairs/ David Nowotnik, Ph.D., Sr. VP, R & D	**From:** Jacquelyn Smith, Project Manager
Company: Access Pharmaceuticals, Inc.	Division of Dermatologic and Dental Drug Products
Fax number: (214) 905-5101	**Fax number:** (301) 827-2075
Phone number: (214) 905-5100	**Phone number:** (301) 827-2027

Subject: NDA 21-727/ (Amlexanox)
Revised Draft Labeling

Total no. of pages including cover: 7

Comments: If you agree with the proposed labeling, please fax us a statement confirming that you agree.
Thank you,
Jacquelyn

Document to be mailed: ☐ YES X NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 301-827-2020. Thank you.

6 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

NDA 21-727
N-000

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

Date: September 21, 2004

To: Amy Campbell, Manager, Regulatory Affairs	**From:** Jacquelyn Smith, Project Manager
Company: Access Pharmaceuticals, Inc.	Division of Dermatologic and Dental Drug Products
Fax number: (214) 905-5101	**Fax number:** (301) 827-2075
Phone number: (214) 905-5100	**Phone number:** (301) 827-2027
Subject: NDA 21-727 (Amlexanox 2mg, Mucoadhesive Patch) Original Submission	
Total no. of pages including cover: 3	

Document to be mailed: ☐ YES X NO

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If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 301-827-2020. Thank you.

NDA 21-727
N-000

FDA Fax Memo

Date: September 21, 2004

Dear Ms. Campbell:

The clinical pharmacology and biopharmaceutics review team has asked that the following comment be conveyed to you.

With regards to in vitro dissolution, the Agency requests you to set an interim dissolution specification of NLT(Q) [ ], of the labeled content of the drug to be dissolved in 60 minutes.

Regards,

Jacquelyn Smith
Project Manager
DDDDP, HFD-540

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jacquelyn Smith
9/21/04 11:46:44 AM
CSO

ORIGINAL

ACCESS
PHARMACEUTICALS, INC.

2600 Stemmons Freeway, Suite 176
Dallas, TX 75207-2107
Tel (214) 905-5100 Fax (214) 905-5101

www.accesspharma.com
e-mail: akc@accesspharma.com

N-000 (82)
ORIG AMENDMENT

September 20, 2004

RECEIVED
SEP 2 1 2004
MEGA/CDER

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12,229 Wilkins Avenue
Rockville, MD 20852

Re: **OraDisc™A (Amlexanox 2mg, Mucoadhesive Patch)**
NDA No. **21-727**
Volume No. **9**

Re: Response to CMC Deficiencies, dated September 13, 2004, and to Labeling Comments in faxes dated August 16, and September 16, 2004

Dear Sir or Madam:

Reference is made to your faxes dated August 16, 2004, September 13, 2004, and September 16, 2004, in which a set of comments were made by the division.

Included in this submission please find the following:

- Response to CMC Deficiencies fax dated September 13, 2004
- Response to Labeling Comments in faxes dated Augusat 16, 2004 and September 16, 2004

As the original NDA submission was presented in the CTD format, this volume and all other volumes will also be presented in the CTD format. The responses and data are located in Module 1 as listed in Section 1.2 "Comprehensive Table of Contents".

If you have any questions or comments, please contact me by phone at (214) 905-5100, by fax at (214) 905-5101, or by e-mail at alc@accesspharma.com.

Sincerely yours,

Amy Campbell

Amy Campbell
Manager, Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Access Pharmaceuticals, Inc.	9/20/04
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(214) 905-5100	(214) 905-5101
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE**
2600 Stemmons Freeway, Suite 176 Dallas, TX 75207-2107	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-727

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY	
Amlexanox 2mg, Mucoadhesive Patch	OraDisc™A	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*		**CODE NAME** *(If any)*
Amlexanox		
DOSAGE FORM:	**STRENGTHS:**	**ROUTE OF ADMINISTRATION:**
Mucoadhesive Patch	2 mg	topical

(PROPOSED) INDICATION(S) FOR USE:
Treatment of Aphthous Ulcers

PRODUCT DESCRIPTION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
new dosage form for the treatment of aphthous ulcers

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See attached List

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND # 59,959: Amlexanox OraDisc
DMF #[redacted] DMF #[redacted]
DMF #[redacted] DMF #[redacted]

RECEIVED
SEP 21 2004

This application contains the following items: *(Check all that apply)*	
☒	1. Index
☒	2. Labeling *(check one)* ☒ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☒	4. Chemistry section
☒	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
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☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
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☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* Response to CMC Reviewer Questions, Response to Labeiling Comments, DMF Reference Letter

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

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7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
David Nowotnik	David P. Nowotnik, Ph.D.; Senior VP Research & Development	9/20/04

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2600 Stemmons Freeway, Suite 176, Dallas, TX 75207-2107	(214) 905-5100

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CBER, HFM-94
1241 Parklawn Dr., Room 3046
Rockville, MD 20852

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

Date: September 16, 2004

To: Amy Campbell, Manager, Regulatory Affairs/ David Nowotnik, Ph.D., Sr. VP, R & D	**From:** Jacquelyn Smith, Project Manager
Company: Access Pharmaceuticals, Inc.	Division of Dermatologic and Dental Drug Products
Fax number: (214) 905-5101	**Fax number:** (301) 827-2075
Phone number: (214) 905-5100	**Phone number:** (301) 827-2027

Subject: NDA 21-727/OraDisc™ A (Amlexanox 2mg, Mucoadhesive Patch) Revised Draft Labeling

Total no. of pages including cover: 9

Comments: Please fax a highlight/strikeout copy, as well as a clean copy incorporating your suggested changes. A tcon will be scheduled as soon as possible to discuss suggested changes.

Document to be mailed: ☐ YES X NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 301-827-2020. Thank you.

Sept. 16, 2004

Attached is your proposed label for OraDisc, which includes suggested revisions that the Agency has made. Please review these changes. Also, please consider revision of the terms [ ] in line 82, and [ ] in line 98, as well as [ ] in line 100. Please propose a more consistent way to describe the disappearance of the disc.

Appears This Way
On Original

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

Date: September 14, 2004

To: Amy Campbell, Manager, Regulatory Affairs	**From:** Jacquelyn Smith, Project Manager
Company: Access Pharmaceuticals, Inc.	Division of Dermatologic and Dental Drug Products
Fax number: (214) 905-5101	**Fax number:** (301) 827-2075
Phone number: (214) 905-5100	**Phone number:** (301) 827-2027
Subject: NDA 21-727/9-3-04 Tcon	
Total no. of pages including cover: 5	

Document to be mailed: ☐ YES X NO

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MEMORANDUM OF TELECON

DATE: September 3, 2004, 10:00 AM

APPLICATION NUMBER: NDA 21-727

DRUG PRODUCT: Amlexanox

BETWEEN:

Name: David P. Nowotnik, Ph.D., Sr. Vice President, Research and Development
Ric Zarzycki, Ph.D., Quality Control and Logistics
Amy Campbell, Manager, Regulatory Affairs

Phone: (214) 905-5100
Representing: Access Pharmaceuticals, Inc.

AND

Name: Division of Dermatologic and Dental Drug Products, HFD-540
David Lin, Ph.D., Supervisor, Chemistry
Norman Schmuff, Ph.D., Acting Deputy Division Director
Felecia Curtis, Regulatory Health Project Manager
Jacquelyn Smith, Regulatory Health Project Manager

SUBJECT: NDA 21-727

A FDA-initiated telecon was held to discuss CMC issues related primarily to dissolution issues arising from the five FAXs from Access sent 8/31/2004. Following are FDA's questions/requests and the firm's responses:
-Why was USP dissolution metric of General Chapter <711> not employed?
--Access responded that they did not know, as this decision was made before participants joined the firm.

-Explain the [t for product]

--Access concluded that there was an error in 8/31/2004 FAX 4 of 5, which inadvertently [ ] They agreed to FAX the corrected data.

-Explain why [ ]for lots 4257, 4258, and 4259 are [ ]

--An investigation is currently underway to determine the cause of this.

-Why was the USP metric for Uniformity of Dosage Units <905> not employed?
--Access responded that they did not know, as this decision was made before participants joined the firm.

FDA indicated that compliance with the two indicated USP chapters would be included in a forthcoming CMC information request.

Addendum:
The corrected dissolution data was received today, September 3, 2004.

The conversation ended amicably.

Appears This Way
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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Norman Schmuff
9/14/04 06:47:37 AM

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jacquelyn Smith
9/14/04 09:13:47 AM
CSO

NDA 21-727
N-000

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

Date: September 13, 2004

To: Amy Campbell, Manager, Regulatory Affairs	**From:** Jacquelyn Smith, Project Manager
Company: Access Pharmaceuticals, Inc.	Division of Dermatologic and Dental Drug Products
Fax number: (214) 905-5101	**Fax number:** (301) 827-2075
Phone number: (214) 905-5100	**Phone number:** (301) 827-2027
Subject: NDA 21-727 (Amlexanox 2mg, Mucoadhesive Patch) Original Submission	
Total no. of pages including cover: 4	

Document to be mailed: ☐ YES X NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

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NDA 21-727
N-000

FDA Fax Memo

Date: September 13, 2004

Dear Ms. Campbell:

Please address the following CMC deficiencies with regard to NDA 21-727. Please respond as soon as possible.

Deficiencies:

1) Please submit the COA of a typical batch of drug substance as tested by Access Pharmaceuticals, Inc. in order to support the statement as indicated in 3.2.S.4.3.

2) Please resolve the discrepancy was observed in the listing of the composition [ ] Instead of reporting Hypromellose (hydroxypropyl methylcellulose) [ ] no amount was given; instead of reporting, no amount for Povidone [ ] was reported, and instead of reporting [ ] no value was given for [ ]

3) Please provide container closure information under Section 2.3.P.7.

   a. The physicochemical tests on the container/closure system should be submitted as per USP requirements.
   b. A description of [ ] and whether this [ ] is permitted for use in drugs.
   c. A description of the [ ] and whether this [ ] is permitted for use in drugs.

4) Please submit in Section 2.3.P.4:

   a. The COAs for the excipients used to manufacture OraDisc™ A, Amlexanox 2 mg Patch.
   b. The analytical methods for the excipients that do not have compendial monographs.

5) Please revise the Specifications for OraDisc™A, Amlexanox 2 mg Patch (2.3.P.5.1) to include the following:

   a. [ ]

   b. A limit for unspecified degradants and total degradants.

c. A content uniformity attribute as per USP 27 < 905> Uniformity of Dosage Units.

d. Module 2 Volume1.1 Section 2.3.P.5.1 contains a misprint in the specification, whereby the specification for [ ] content and dissolution is incorrectly stated. In this regard, the dissolution specification should indicate [ ] for Amlexanox Released in 60 min.; the specification for [ ] should indicates [ ]

e. The use of the USP 27 < 711> metric for dissolution testing, including the acceptance criteria for S_1, S_2, and S_3 stages.

f. A discrepancy was reported in COAs specification for [ ] (see Module 3 Volume 1.4 Section 3.2P.5.4.1), whereby a value of NMT [ ] was reported instead of [ ] as shown in Table 2.3.P.5-1 specification.

6) Under the Analytical Procedures for OraDisc™A, Amlexanox 2 mg Patch (2.3.P.5.2), the following information should be submitted:

a. System suitability for the HPLC method.

b. A correction of the discrepancy for test methods [ ] which are reported as dissolution and content (assay), respectively in table 2.3.5.1 and as the reverse in the validation report.

7) Under Stability for OraDisc™A, Amlexanox 2 mg Patch (2.3.P8), the following information should be submitted:

a. Ongoing stability data [ ] when available.

b. An explanation for why [ ] Was an investigation conducted?

Regards,

Jacquelyn Smith
Project Manager
DDDDP, HFD-540

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jacquelyn Smith
9/13/04 03:07:28 PM
CSO

MEMORANDUM OF TELECON

DATE: September 3, 2004, 10:00 AM

APPLICATION NUMBER: NDA 21-727

DRUG PRODUCT: Amlexanox

BETWEEN:

Name: David P. Nowotnik, Ph.D., Sr. Vice President, Research and Development
Ric Zarzycki, Ph.D., Quality Control and Logistics
Amy Campbell, Manager, Regulatory Affairs

Phone: (214) 905-5100
Representing: Access Pharmaceuticals, Inc.

AND

Name: Division of Dermatologic and Dental Drug Products, HFD-540
David Lin, Ph.D., Supervisor, Chemistry
Norman Schmuff, Ph.D., Acting Deputy Division Director
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Jacquelyn Smith, Regulatory Health Project Manager

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]

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Norman Schmuff
9/14/04 06:47:37 AM

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/s/

Mary Jean Kozma Fornaro
12/9/03 10:09:33 AM

ACCESS
PHARMACEUTICALS, INC.

2600 Stemmons Freeway, Suite 176
Dallas, TX 75207-2107
Tel (214) 905-5100 Fax (214) 905-5101

www.accesspharma.com
e-mail: akc@accesspharma.com

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August 30, 2004

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Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12,229 Wilkins Avenue
Rockville, MD 20852

Re: OraDisc™A (Amlexanox 2mg, Mucoadhesive Patch)
NDA No. 21-727
Volume No. 8

N-000(BC)
ORIG AMENDMENT

Re: Response to Chemistry Reviewer's Questions, dated August 24, 2004; Method Validation for In-Process Amlexanox Content

Dear Sir or Madam:

Reference is made to your Fax dated August 24, 2004, in which a set of requests was made by the chemistry reviewer.

Included in this submission please find:

- Responses to the Chemistry Reviewer's questions in the Fax of August 24, 2004.
- Requested dissolution data for stability data submitted in the Interim Stability Report, [ ]
- Final Method and Method Validation Report for the In-Process Amlexanox Content of the Mucoadhesive Paste.

As the original NDA submission was presented in the CTD format, this volume and all other volumes will also be presented in the CTD format. The responses and data are located in Module 1 as listed in Section 1.2 "Comprehensive Table of Contents".

If you have any questions or comments, please contact me by phone at (214) 905-5100, by fax at (214) 905-5101, or by e-mail at alc@accesspharma.com.

Sincerely yours,

Amy Campbell

Amy Campbell
Manager, Regulatory Affairs

ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Access Pharmaceuticals, Inc.	8/30/04
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(214) 905-5100	(214) 905-5101
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
2600 Stemmons Freeway, Suite 176 Dallas, TX 75207-2107	RECEIVED SEP 0 1 2004 CDR / CDER

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-727

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Amlexanox 2mg, Mucoadhesive Patch	OraDisc™A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Amlexanox	

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Mucoadhesive Patch	2 mg	topical

(PROPOSED) INDICATION(S) FOR USE:
Treatment of Aphthous Ulcers

PRODUCT DESCRIPTION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
new dosage form for the treatment of aphthous ulcers

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

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See attached List

ORIGINAL

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IND # 59,959: Amlexanox OraDisc
DMF #[redacted]
DMF #[redacted]
DMF #[redacted]

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SEP 0 2 2004
MEGA/CDER

Created by Media Arts/USDHHS: (301) 443-2454 EF

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6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
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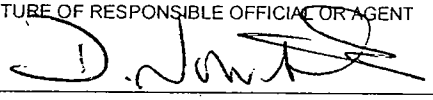
Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
	David P. Nowotnik, Ph.D.; Senior VP Research & Development	8/30/04

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2600 Stemmons Freeway, Suite 176, Dallas, TX 75207-2107	(214) 905-5100

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Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CBER, HFM-94
1242? Parklawn Dr., Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

1.1 Form 356(h) Establishment Information

Company Name	Access Pharmaceuticals, Inc.
Address	2600 Stemmons Freeway
	Suite 176
	Dallas, TX 75207-2107
Contact	Ric Zarzycki, Ph.D. Director of Quality
Phone	(214) 905-5100
Activities at site	Finished product release testing, finished product stability testing
Inspection readiness	Ready for Inspection

NDA 21-727
N-000

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

Date: August 24, 2004

To: Amy Campbell, Manager, Regulatory Affairs	**From:** Jacquelyn Smith, Project Manager
Company: Access Pharmaceuticals, Inc.	Division of Dermatologic and Dental Drug Products
Fax number: (214) 905-5101	**Fax number:** (301) 827-2075
Phone number: (214) 905-5100	**Phone number:** (301) 827-2027
Subject: NDA 21-727/OraDisc™ A (Amlexanox 2mg, Mucoadhesive Patch) Original Submission	
Total no. of pages including cover: 3	

Document to be mailed: ☐ YES X NO

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ACCESS
PHARMACEUTICALS, INC.

2600 Stemmons Freeway, Suite 176
Dallas, TX 75207-2107
Tel (214) 905-5100 Fax (214) 905-5101

www.accesspharma.com
e-mail: akc@accesspharma.com

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August 30, 2004

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Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12,229 Wilkins Avenue
Rockville, MD 20852

Re: OraDisc™A (Amlexanox 2mg, Mucoadhesive Patch)
NDA No. 21-727
Volume No. 8

N-000(BC)
ORIG AMENDMENT

Re: Response to Chemistry Reviewer's Questions, dated August 24, 2004; Method Validation for In-Process Amlexanox Content

Dear Sir or Madam:

Reference is made to your Fax dated August 24, 2004, in which a set of requests was made by the chemistry reviewer.

Included in this submission please find:

- Responses to the Chemistry Reviewer's questions in the Fax of August 24, 2004.
- Requested dissolution data for stability data submitted in the Interim Stability Report, [ ]
- Final Method and Method Validation Report for the In-Process Amlexanox Content of the Mucoadhesive Paste.

As the original NDA submission was presented in the CTD format, this volume and all other volumes will also be presented in the CTD format. The responses and data are located in Module 1 as listed in Section 1.2 "Comprehensive Table of Contents".

If you have any questions or comments, please contact me by phone at (214) 905-5100, by fax at (214) 905-5101, or by e-mail at alc@accesspharma.com.

Sincerely yours,

Amy Campbell

Amy Campbell
Manager, Regulatory Affairs

ORIGINAL

NDA 21-727
N-000

FDA Fax Memo

Date: August 24, 2004

Dear Ms. Campbell:

Chemistry has asked that the following comments be conveyed to you.

1) The proposed tentative expiration of 12 months at 25 deg C is acceptable provided that a cautionary statement against prolonged exposure at or above 30 deg C is added to the labeling. All of the labeling should be revised to include the following information:

Store at 25 deg C (77 deg F)

[Caution: Avoid prolonged exposure to temperatures above 30 deg C]

2) The storage statement of indicating suggested storage at [ ] is not acceptable both because of reasons stated above, and because no stability data were submitted to support refrigerated conditions. In this regard, please submit a revised stability protocol, and the data derived from these stability studies to support refrigerated conditions. All tests attributes as submitted under the Interim Stability Testing Report, [ ] dated 7/25/03 should also be included in the revised stability protocol.

3) Please submit individual tests results (i.e. the per cent dissolved for each individual unit, and the number of units tested) for the dissolution studies described in the Interim Stability Testing Report, [ ] dated 7/25/03 for Amlexanox OraDisc, 2 mg, Lot # 4257, 4258 and 4259.

Please respond as soon as possible. If you have any questions, please contact me at 301-827-2027.

Sincerely,

Jacquelyn Smith
Project Manager
DDDDP, HFD-540

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/s/

Jacquelyn Smith
8/24/04 02:12:33 PM
CSO

NDA 21-727
N-000

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

Date: August 16, 2004

To: Amy Campbell, Manager, Regulatory Affairs	**From:** Jacquelyn Smith, Project Manager
Company: Access Pharmaceuticals, Inc.	Division of Dermatologic and Dental Drug Products
Fax number: (214) 905-5101	**Fax number:** (301) 827-2075
Phone number: (214) 905-5100	**Phone number:** (301) 827-2027

Subject: NDA 21-727/Tradename comments

Total no. of pages including cover: 7

Comments: Please find below comments regarding TRADENAME "OraDisc A".

Document to be mailed: ☐ YES X NO

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NDA 21-727
N-000

FDA Fax Memo

DMETS does not recommend the use of the proprietary name OraDisc A. In reviewing the proprietary name, the primary concerns related to look-alike and/or sound-alike confusion with Orudis KT. Include only the names that had the potential for confusion.

A. Look-Alike/Sound-Alike Issues

1. OraDisc A and Orudis KT can sound similar when pronounced and look similar when scripted. Orudis KT is a nonsteroidal anti-inflammatory agent indicated for temporary relief of minor aches and pains associated with common cold, headache, toothache, muscular aches, backache, minor arthritis pain, menstrual cramps, and reduction of fever. Since both products will only be available as OraDisc A and Orudis KT, the modifiers may be omitted by prescribers, thus the potential for sound-alike and look-alike confusion between OraDisc and Orudis is increased. This is possible since the modifiers do not provide any differentiating product characteristics. Timothy S. Lesar, PharmD conducted research at a 631-bed teaching hospital in order to evaluate prescribing errors involving medication dosage forms. Analysis of 402 medication errors that occurred over a 16-month period (Sept. 1999 – Dec. 2000) demonstrated that the most common error was due to the failure to specify a controlled-release dosage formulation through the use of a modifier (280 cases or 69.7%).[1] Studies such as this one support DMETS' concern that healthcare professionals my omit modifiers. OraDisc and Orudis both begin with the letters 'Or' and end with similar letters ('aDisc' vs. 'udis') which account for the orthographic and phonetic similarities of the names. Although the strengths are different, this may not help to distinguish the two products from each other. OraDisc and Orudis are only available in one strength; therefore the strength can be omitted from a prescription and still be dispensed because it is not required to verify a product selection. The two products also share the same frequency of administration (every 6 hours), overlap in route of administration (oral), and can overlap in quantity dispensed (20). Therefore prescriptions can be called in or written in a similar manner (e.g. "OraDisc, use as directed every 6 hours" vs. "Orudis, use as directed every 6 hours"). The sound-alike and look-alike characteristics, as well as the overlapping product characteristics increase the potential for medication errors between this name pair.

Oradisc Orudis

[1] Lesar, Timothy S. Prescribing Errors involving Medication Dosage Forms. J Gen. Intern. Med.2002;17:579-87.

2. OraDisc A can look similar to Oralone when scripted. Oralone is a corticosteroid used to treat the swelling and discomfort of the mouth and gums. OraDisc A is the only available dosage form of this product. Thus the modifier may be omitted by prescribers increasing the potential for look-alike confusion between OraDisc and Oralone. This is because the modifier 'A' does not provide any differentiating product characteristics. OraDisc and Oralone both begin with the same three letters, 'Ora,' which is the principal contribution to the look-alike characteristics of the names. Additionally, the endings of each name can look similar as well. The upstroke of the letter 'D' can resemble the letter 'l' especially if the letter 'D' is written in lower case. Furthermore, 'isc' can look similar to 'one,' depending on how it is scripted (see page 6). Since OraDisc and Oralone are only available in one strength, the strength can be omitted from a prescription and still be dispensed. Additionally, due to the nature of both products being used on an "as needed" basis for acute conditions and not used continuously for chronic conditions, it is not uncommon for the directions of the prescription to be "use as directed." Therefore it is possible to see prescriptions such as, "OraDisc, use as directed," or "Oralone, use as directed." Both products overlap in route of administration (oral) and will most likely be stored near each other on the pharmacy shelf. Therefore, the look-alike characteristics, along with the lack of distinguishing product characteristics, allow for an increased risk for medication errors due to name confusion.

3. OraDisc A can sound similar to Oraqix when pronounced. Oraqix is an anesthetic indicated for adults who require localized anesthesia in periodontal pockets during scaling and/or root planing. The beginnings of OraDisc A and Oraqix are identical ('Ora'), which is the principal contribution to the sound-alike similarities of the names. Additionally, the endings ('Disc' vs. 'qix') can sound similar. OraDisc A is the only dosage form of this product. Thus the modifier may be omitted by prescribers increasing the potential for look-alike confusion between OraDisc and Oralone. This is because the modifier 'A' does not provide any differentiating product characteristics. Although OraDisc and Oraqix have different dosage forms (mucoadhesive patch vs. periodontal gel), they will both be applied to the affected area of the mouth. Oraqix is intended to be used by dental professionals for use during dental procedures, and therefore, is generally not dispensed directly to patients. However, OraDisc A may be stocked in a dentist's office in addition to being available by prescription. The sound-alike similarities between OraDisc A and Oraqix and the conditions of use increase the potential for medication errors due to name confusion between OraDisc A and Oraqix.

B. Nomenclature Issues

Through further research on publicly accessible web sites, DMETS has learned that OraDisc is in fact a technology employing an erodible patch which adheres to the mucosal surface of the oral cavity for local drug delivery, or drug delivery to the systemic circulation. Additionally, the sponsor has already developed a benzocaine formulation using the OraDisc technology, which is listed on the website as OraDisc B. The standard practice for using names containing a technology or dosage from is to use the technology name or dosage form as a modifier (e.g. Zyprexa Zydis, Claritin Reditabs, Risperdal M-Tabs, etc.). It appears that the sponsor is doing the opposite, and using the technology name as the root name, and only using a single letter modifier ('A' or 'B') to indicate the active ingredient. Therefore, the same root name ('OraDisc') will be used for different active ingredients. This nomenclature practice could cause a proliferation of the name OraDisc in the marketplace, and may lead to confusion especially when the modifier that identifies the active ingredient is omitted or confused when scripted. Therefore, DMETS does not recommend the use of a technology as the root name of a product.

C. Labeling, Packaging, and Safety Related Issues:

In the review of the container labels, carton and insert labeling of OraDisc A, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

1. CONTAINER LABEL

a. Some of the letters (e.g. 'Di') in the proprietary name appear too close together (see below), making it difficult to read. Additionally, the different shades of boxing used around the name dissect the letter 'A' of 'Ora' in half, making the name difficult to read as well. Revise accordingly.

b. Ensure the established name is at least one-half the size of the proprietary name.

2. INSERT LABELING

a. General Comments

Throughout the package insert, the medication is referred to in several different ways, (i.e. OraDisc A, Amlexanox OraDisc, and Amlexanox OraDisc A). Please use either the proprietary name (OraDisc A) or the established name (Amlexanox Patch) when referring to the medication in order to avoid confusion.

b. PRECAUTIONS – Information for Patients Subsection

i. Instruction Number 1:

- Instruct patients to wash their hands before applying OraDisc A.
- Patients are instructed to apply OraDisc A [redacted] before bedtime in order to, "avoid the possibility of aspiration of soft, food-like particles that may come loose…" However, the patch may take up to 80 minutes to dissolve. Please advise patients to apply OraDisc A at least 80 minutes (e.g. an hour and a half) before bedtime, in order to allow time for the patch to completely dissolve.

ii. Instruction Number 2:

- Indicate up to how many patches may be used at one time.

iii. Instruction Number 3:

- Instruct patients what to do if the patch does not adhere readily.

iv. Instruction Number 5:

- Specify what is meant my particles in the statement, "…to ensure that no particles come loose during sleep."

- See second comment under Number 1.

c. The information provided in the Precautions section, Information for Patients, must be reprinted at the end of the labeling per CFR 201.57(f)(2). Revise accordingly.

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/s/

Jacquelyn Smith
8/16/04 01:24:43 PM
CSO

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AUG 17 2004
CDR/CDER

August 13, 2004

N-000(SU)

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12,229 Wilkins Avenue
Rockville, MD 20852

ORIG AMENDMENT

Re: OraDisc™A (Amlexanox 2mg, Mucoadhesive Patch)
NDA No. 21-727
Volume No. 7

Re: 4-month Safety Update Report

Dear Sir or Madam:

Included in this submission please find the 4-month Safety Update Report. As the original NDA submission was presented in the CTD format, this volume and all other volumes will also be presented in the CTD format. The safety update is located in Module 1, Section 1.3.10.

If you have any questions or comments, please contact me by phone at (214) 905-5100, by fax at (214) 905-5101, or by e-mail at alc@accesspharma.com.

Sincerely yours,

Amy Campbell

Amy Campbell
Manager, Regulatory Affairs

ORIGINAL

4 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

✓ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

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N.000(C)

June 8, 2004

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Jonathon Wilkin, M.D.
Division of Dermatologic and Dental Products, HFD-540
Food and Drug Administration
9201 Corporate Blvd.,
Rockville, MD 20850

LETTER OF AUTHORIZATION

NEW CORRESP

NDA 21-727
OraDisc A, 2mg Mucoadhesive Patch
Volume: N/A – general correspondence

Dear Dr. Wilkin,

In reference to a recent telephone call from Ms. Jacquelyn Smith to Access, Access Pharmaceuticals authorizes the agency to use any information contained in NDA 20-511, Aphthasol®, 5% Oral Paste, in the agency's review of NDA 21-727, OraDisc A, 2mg Mucoadhesive Patch.

Sincerely,

David P. Nowotnik, Ph.D.
Snr. V.P., Research & Development

ACCESS
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www.accesspharma.com
e-mail: akc@accesspharma.com

June 2, 2004

Jonathon Wilkin, M.D.
Division of Dermatologic and Dental Products, HFD-540
Food and Drug Administration
9201 Corporate Blvd.,
Rockville, MD 20850

LETTER OF AUTHORIZATION

NDA 21-727
OraDisc A, 2mg Mucoadhesive Patch
Volume: N/A – general correspondence

Dear Dr. Wilkin,

In reference to the telephone call earlier today to Access by Ms. Jacquelyn Smith, Access Pharmaceuticals authorizes the use of the chemistry, manufacturing and controls information in NDA 20-511, Aphthasol®, 5% Oral Paste, in the agency's review of NDA 21-727, OraDisc A, 2mg Mucoadhesive Patch.

If you have any further requests, or require any additional information, please do not hesitate in contacting me.

Sincerely,

David P. Nowotnik, Ph.D.
Snr. V.P., Research & Development

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

Date: June 1, 2004

To: Amy Campbell, Manager, Regulatory Affairs	**From:** Jacquelyn Smith, Project Manager
Company: Access Pharmaceuticals, Inc.	Division of Dermatologic and Dental Drug Products
Fax number: (214) 905-5101	**Fax number:** (301) 827-2075
Phone number: (214) 905-5100	**Phone number:** (301) 827-2027
Subject: NDA 21-727/OraDisc™ A (Amlexanox 2mg, Mucoadhesive Patch) 5/28/04 tcon	
Total no. of pages including cover: 4	

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MEMORANDUM OF TELECON

DATE: May 28, 2004, 9:35 AM

APPLICATION NUMBER: NDA 21-727

DRUG PRODUCT: OraDisc™ (Amlexanox 2mg, Mucoadhesive Patch)

BETWEEN:

Name: Amy L. Campbell, Manager, Regulatory Affairs
Christiane M. Baud, Ph.D., Vice President, Clinical Development

Phone: (214) 905-5100
Representing: Access Pharmaceuticals, Inc.

AND

Name: Division of Dermatologic and Dental Drug Products, HFD-540
John V. Kelsey, D.D.S., M.B.A, Dental Team Leader
Frederick Hyman, D.D.S., M.P.H., Dental Officer
Jacquelyn Smith, Regulatory Project Manager

The FDA contacted the Sponsor regarding their NDA submission that is currently under review, including their submission of April 16, 2004 in which [redacted]. The Agency said that after extensive discussion it had been decided that the additional studies would not be required and that the Agency could complete its review without them. The review will proceed and if the Agency requires additional information, it will contact the Sponsor.

The conversation ended amicably.

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/s/

John Kelsey
5/28/04 02:45:27 PM

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/s/

Jacquelyn Smith
6/1/04 08:39:14 AM
CSO

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

Date: May 17, 2004

To: Amy Campbell, Manager, Regulatory Affairs	**From:** Jacquelyn Smith, Project Manager
Company: Access Pharmaceuticals, Inc.	Division of Dermatologic and Dental Drug Products
Fax number: (214) 905-5101	**Fax number:** (301) 827-2075
Phone number: (214) 905-5100	**Phone number:** (301) 827-2027
Subject: NDA 21-727/OraDisc™ A (Amlexanox 2mg, Mucoadhesive Patch) 050404 tcon	
Total no. of pages including cover: 4	

Document to be mailed: ☐ YES X NO

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MEMORANDUM OF TELECON

DATE: May 4, 2004, 2:30 PM

APPLICATION NUMBER: NDA 21-727

DRUG PRODUCT: OraDisc™ A (Amlexanox 2mg, Mucoadhesive Patch)

BETWEEN:

Name: David P. Nowotnik, Ph.D., Sr. Vice President, Research & Development,
Christiane M. Baud, Ph.D., Vice President, Clinical Development

Phone: (214) 905-5100
Representing: Access Pharmaceuticals, Inc.

AND

Name: Division of Dermatologic and Dental Drug Products, HFD-540
John V. Kelsey, D.D.S., M.B.A, Dental Team Leader
Frederick Hyman, D.D.S., M.P.H., Dental Officer
Jacquelyn Smith, Regulatory Project Manager

SUBJECT: New Protocol

In a teleconference, on March 26, 2004, the Agency requested that the Sponsor propose a [redacted] This study would involve a [redacted]. The Sponsor stated that a complete clinical study plan for the clinical study would be submitted within two weeks. The Sponsor submitted this new protocol to the Agency on April 16, 2004.

In today's teleconference, the Agency requested more time to review the protocol. The Sponsor agreed to the Agency's request since the Sponsor is not ready to begin the clinical study.

The conversation ended amicably.

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/s/

John Kelsey
5/17/04 02:22:26 PM

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/s/

Jacquelyn Smith
5/17/04 02:36:45 PM
CSO

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e-mail: AKC@accesspharma.com

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March 24, 2004

N-600(Rim)
ORIG AMENDMENT

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MAR 2 9 2004
DDR-110 / CDER

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MAR 2 9 2004
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Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12,229 Wilkins Avenue
Rockville, MD 20852

Re: **OraDisc™A (Amlexanox 2mg, Mucoadhesive Patch)**
NDA No. **21-727**
Volume No. **6**

Re: Response to Clinical Reviewer's Question, dated March 22, 2004

Dear Sir or Madam:

Reference is made to your fax dated March 22, 2004, in which a question about patient enrollment was made by the clinical reviewer.

Included in this submission please find the response to the Clinical Reviewer's question in the fax of March 22, 2004. As the original NDA submission was presented in the CTD format, this volume and all other volumes will also be presented in the CTD format. The response is located in Module 1 as listed in Section 1.2 "Submission Volume 6 Table of Contents".

If you have any questions or comments, please contact me by phone at (214) 905-5100, by fax at (214) 905-5101, or by e-mail at alc@accesspharma.com.

Sincerely yours,

Amy Campbell

Amy Campbell
Manager, Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Access Pharmaceuticals, Inc.	3/24/04
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(214) 905-5100	(214) 905-5101
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE**
2600 Stemmons Freeway, Suite 176 Dallas, TX 75207-2107	RECEIVED MAR 2 6 2004 CDR / CDER

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-727

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Amlexanox 2mg, Mucoadhesive Patch	OraDisc™A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Amlexanox	

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Mucoadhesive Patch	2 mg	topical

(PROPOSED) INDICATION(S) FOR USE:

ıtment of Aphthous Ulcers

..ODUCT DESCRIPTION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

new dosage form for the treatment of aphthous ulcers

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See attached List

RECEIVED
MAR 2 9 2004

s References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMEs referenced in the current application)

DDR-110 / CDER

IND # 59,959: Amlexanox OraDisc
DMF #
DMF #
DMF #

RECEIVED
MAR 2 9 2004
MEGA/CDER

Created by Media Arts/USDHHS (301) 443-2410 ET

This application contains the following items: *(Check all that apply)*

☑	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* Response to Clinical Reviewer Question dated March 22, 2004

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
D. Nowotnik	David P. Nowotnik, Ph.D.; Senior VP Research & Development	3/24/04

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2600 Stemmons Freeway, Suite 176, Dallas, TX 75207-2107	(214) 905-5100

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. nd comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

rtment of Health and Human Services
od and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CBER, HFM-94
12420 Parklawn Dr., Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

1.1 Form 356(h) Establishment Information

Company Name	Access Pharmaceuticals, Inc.
Address	2600 Stemmons Freeway
	Suite 176
	Dallas, TX 75207-2107
Contact	Ric Zarzycki, Ph.D. Director of Quality
Phone	(214) 905-5100
Activities at site	Finished product release testing, finished product stability testing
Inspection readiness	Ready for Inspection

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

Date: March 22, 2004

To: Amy Campbell, Manager, Regulatory Affairs	**From:** Jacquelyn Smith, Project Manager
Company: Access Pharmaceuticals, Inc.	Division of Dermatologic and Dental Drug Products
Fax number: (214) 905-5101	**Fax number:** 301-827-2075
Phone number: (214) 905-5100	**Phone number:** 301-827-2027

Subject: NDA 21-727/OraDisc

Total no. of pages including cover: 2

Comments:

Document to be mailed: ☐ YES X NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 301-827-2020. Thank you.

March 22, 2004

Dear Ms Campbell:

Per our discussion by telephone this morning, I am faxing this request for information from our review team with regard to NDA 21-727/OraDisc.

In the process of reviewing the data submitted with NDA 21-727, the Agency is evaluating not only trial 1U106, but the earlier clinical trials as well. In the process of review, we noticed that there were 7 investigators who participated in both studies 1U106 and 9E03. [ ]
The patient enrollment for these investigators accounts for about 27.4% (192/701) and 49.6% (199/401) of the total enrollment in studies 1U106 and 9E03, respectively. Could you tell us how many of those 192 subjects in study 1U106 were also subjects in study 9E03?

Appears This Way
On Original

ACCESS
PHARMACEUTICALS, INC.

ORIGINAL

2600 Stemmons Freeway, Suite 176
Dallas, TX 75207-2107
Tel (214) 905-5100 Fax (214) 905-5101

www.accesspharma.com
e-mail: AKC@accesspharma.com

N-000(B2)
ORIG AMENDMENT

March 15, 2004

RECEIVED
MAR 16 2004
CDR / CDER

RECEIVED
MAR 17 2004
MEGA/CDER

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12,229 Wilkins Avenue
Rockville, MD 20852

Re: **OraDisc™A (Amlexanox 2mg, Mucoadhesive Patch)**
NDA No. **21-727**
Volume No. **5**

Re: Response to Clinical Reviewer's Questions, dated February 20, 2004

Dear Sir or Madam:

Reference is made to your Filing Review Letter dated February 20, 2004, in which a set of requests was made by the reviewers.

Included in this submission please find the responses to the Clinical and Biostatistics Reviewers' questions in the Filing Review Letter of February 20, 2004. As the original NDA submission was presented in the CTD format, this volume and all other volumes will also be presented in the CTD format. The response is located in Module 1 and the report is located in Module 5, as listed in Section 1.2 "Volume 5.1 Table of Contents".

If you have any questions or comments, please contact me by phone at (214) 905-5100, by fax at (214) 905-5101, or by e-mail at alc@accesspharma.com.

Sincerely yours,

Amy Campbell

Amy Campbell
Manager, Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

ORIGINAL

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

RECEIVED
MAR 17 2004
MEGA/CDER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Access Pharmaceuticals, Inc.	3/15/04
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(214) 905-5100	(214) 905-5101
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
2600 Stemmons Freeway, Suite 176 Dallas, TX 75207-2107	

N-609 (132)
ORIG AMENDMENT

RECEIVED
MAR 16 2004
CDR / CDER

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-727

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY	
Amlexanox 2mg, Mucoadhesive Patch	OraDisc™A	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*		**CODE NAME** *(If any)*
Amlexanox		
DOSAGE FORM:	**STRENGTHS:**	**ROUTE OF ADMINISTRATION:**
Mucoadhesive Patch	2 mg	topical

(PROPOSED) INDICATION(S) FOR USE:

tment of Aphthous Ulcers

PRODUCT DESCRIPTION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

new dosage form for the treatment of aphthous ulcers

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See attached List

References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

NDA # 59,959: Amlexanox OraDisc
DMF #
DMF #
DMF #

Created by Media Arts/USDHHS: (301) 443-2454 EF

's application contains the following items: *(Check all that apply)*

☑	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☑	17. Field copy certification (21 CFR 314.50 (l)(3))
☑	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* Answers to Clinical and Biostatics Questions

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
David Nowotnik	David P. Nowotnik, Ph.D.; Senior VP Research & Development	3/15/04

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2600 Stemmons Freeway, Suite 176, Dallas, TX 75207-2107	(214) 905-5100

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. ı comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

.rtment of Health and Human Services
'ood and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CBER, HFM-94
12420 Parklawn Dr., Room 3046
Rockville, MD 20852

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1.1 Form 356(h) Establishment Information

Company Name	Access Pharmaceuticals, Inc.
Address	2600 Stemmons Freeway
	Suite 176
	Dallas, TX 75207-2107
Contact	Ric Zarzycki, Ph.D. Director of Quality
Phone	(214) 905-5100
Activities at site	Finished product release testing, finished product stability testing
Inspection readiness	Ready for Inspection

ACCESS
PHARMACEUTICALS, INC.

2600 Stemmons Freeway, Suite 176
Dallas, TX 75207-2107
Tel (214) 905-5100 Fax (214) 905-5101

www.accesspharma.com
e-mail: AKC@accesspharma.com

RECEIVED
MAR 01 2004
CDR/CDER

RECEIVED
MAR 02 2004
MEGA/CDER

February 27, 2004

Recode N-021 SE
PER PM 3-5-04
N-000 (BE)(BZ)
ORIG AMENDMENT

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12,229 Wilkins Avenue
Rockville, MD 20852

Re: OraDisc™A (Amlexanox 2mg, Mucoadhesive Patch)
NDA No. 21-727
Volume No. 4

Re: Response to Chemistry Reviewer's Questions, dated February 20, 2004

Dear Sir or Madam:

Reference is made to your Filing Review Letter dated February 20, 2004, in which a set of requests was made by the reviewers.

Included in this submission please find the responses to the Chemistry Reviewer's questions in the Filing Review Letter of February 20, 2004. As the original NDA submission was presented in the CTD format, this volume and all other volumes will also be presented in the CTD format. The responses and data are located in Module 1 as listed in Section 1.2 "Comprehensive Table of Contents".

If you have any questions or comments, please contact me by phone at (214) 905-5100, by fax at (214) 905-5101, or by e-mail at alc@accesspharma.com.

Sincerely yours,

Amy Campbell

Amy Campbell
Manager, Regulatory Affairs

ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

N 000 (BZ)

ORIG AMENDMENT

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Access Pharmaceuticals, Inc.	2/27/04
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(214) 905-5100	(214) 905-5101
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
2600 Stemmons Freeway, Suite 176 Dallas, TX 75207-2107	RECEIVED MAR 02 2004 MEGA/CDER RECEIVED MAR 01 2004 CDR/CDER

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-727

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Amlexanox 2mg, Mucoadhesive Patch	OraDisc™A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Amlexanox	

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Mucoadhesive Patch	2 mg	topical

(PROPOSED) INDICATION(S) FOR USE:
Treatment of Aphthous Ulcers

ODUCT DESCRIPTION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
new dosage form for the treatment of aphthous ulcers

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

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Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See attached List

ORIGINAL

ss References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

D # 59,959: Amlexanox OraDisc
DMF #
DMF #
DMF #

Created by Media Arts/USDHHS: (301) 443-2454 EF

This application contains the following items: *(Check all that apply)*

☒	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
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☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
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☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
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☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
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☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* EA Waiver Information, Response to CMC Reviewer Questions

CERTIFICATION

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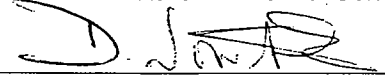
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
	David P. Nowotnik, Ph.D.; Senior VP Research & Development	2/27/04

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2600 Stemmons Freeway, Suite 176, Dallas, TX 75207-2107	(214) 905-5100

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

artment of Health and Human Services
od and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CBER, HFM-94
12420 Parklawn Dr., Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

Date: February 20, 2004

To: Amy Campbell, Manager, Regulatory Affairs	**From:** Jacquelyn Smith, Project Manager
Company: Access Pharmaceuticals, Inc.	Division of Dermatologic and Dental Drug Products
Fax number: (214) 905-5101	**Fax number:** 301-827-2075
Phone number: (214) 905-5100	**Phone number:** 301-827-2027

Subject: NDA 21-727/OraDisc filing review letter

Total no. of pages including cover: 5

Comments:

Document to be mailed: ☐ YES X NO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING REVIEW LETTER

NDA 21-727

Access Pharmaceuticals, Inc.
Attention: David P. Nowotnik, Ph.D.
Senior VP, Research & Development
2600 Stemmons Freeway, Suite 176
Dallas, TX 75207-2107

Dear Dr. Nowotnik:

Please refer to your December 4, 2003, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for, OraDisc™ A (amlexanox) Mucoadhesive Patch, 2mg.

We also refer to your submissions dated December 12, 2003, January 8 and 30, 2004 and February 3, 2004.

We have completed our filing review, and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on February 6, 2004, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

Chemistry, Manufacturing and Controls:

1. No environmental assessment or request for categorical exclusion has been provided.
2. We cannot locate data requested by the Division during the IND phase & pre-NDA meeting.
3. We cannot locate the Investigational Formulations information.
4. Desk copies of volumes 1.3, 1.4 and 1.5 to PHL-DO for the use of the inspector cannot be located and have been requested.

Clinical:

1. In Study AC-P-1U106, your reported results for the primary outcome variable show a statistically significant improvement on Day 5. However, at Day 7 this trend reversed.
2. In Study AC-P-1U106, the secondary endpoint, pain relief, shows no statistically significant improvement in the OraDisc at Day 5, or at any other day compared to vehicle patch.

Biostatistics:

1. There are no subgroup results of the primary efficacy endpoint by age (pediatric, adult, and geriatric), gender, race, baseline number of ulcers treated, baseline ulcer size, and baseline pain score for both intent-to-treat and efficacy evaluable populations.

We request that you submit the following information to address the potential review issues described above:

Chemistry, Manufacturing and Controls:

1. Please provide an environmental assessment or, if you intend to request a categorical exclusion, please provide the calculations to support the categorical exclusion.
2. Please identify where all data requested by the division during the IND phase & pre-NDA meeting can be found in the NDA.
3. Please indicate where the Investigational Formulations information can be found in the NDA.
4. Please forward desk copies of volumes 1.3, 1.4 and 1.5 to PHL-DO for the use of the inspector, as requested by telephone on February 17, 2004.

Clinical:

1. Please provide any explanation for why the trend for the primary outcome variable reverses on Day 7, with the vehicle patch showing a better outcome than the OraDisc.
2. Please provide any rationale for not seeing an improvement in pain scores.

Biostatistics:

1. For each of studies 1U106 and 9E03, please submit subgroup results of the primary efficacy endpoint by age (pediatric, adult, and geriatric), gender, race, baseline number of ulcers treated, baseline ulcer size, and baseline pain score for both intent-to-treat and efficacy evaluable populations.

Please respond to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Jacquelyn Smith, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Jonathan Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Stanka Kukich
2/20/04 01:58:29 PM
Sign off for Dr. Jonathan Wilkin, Division Director

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED:	**DESIRED COMPLETION DATE:**	**ODS CONSULT #:** 04-0048
February 13, 2004	July 19, 2004 **PDUFA DATE :** October 8, 2004	

TO: Jonathan Wilikin, MD
Director, Division of Dermatologic and Dental Drug Products
HFD-540

THROUGH: Jacquelyn Smith
Project Manager
HFD-540

PRODUCT NAME:	**NDA SPONSOR:** Access Pharmaceuticals, Inc.
Oradisc™ A (Amlexanox Patch) 2 mg **NDA#:** 21-727	

SAFETY EVALUATOR: Kristina C. Arnwine, PharmD

RECOMMENDATIONS:

1. DMETS does not recommend the use of the proprietary name, OraDisc™ A.

2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review in order to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary name OraDisc acceptable from a promotional perspective.

4. DMETS recommends contacting Dr. Guirag Poochikian, Acting Chair of the CDER Labeling and Nomenclature Committee (LNC) regarding the established name of OraDisc™ A.

Carol Holquist, RPh
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: April 7, 2004

NDA#: 21-727

NAME OF DRUG: OraDisc™ A (Amlexanox Patch) 2 mg

NDA HOLDER: Access Pharmaceuticals

I. INTRODUCTION:

This consult was written in response to a request from the Division of Dermatologic and Dental Drug Products (HFD-540), for assessment of the proprietary name, OraDisc™ A, regarding potential name confusion with other proprietary and/or established drug names. Container labels and insert labeling were provided for review and comment.

PRODUCT INFORMATION
OraDisc™ is a mucoadhesive patch that contains 2 mg of amlexanox per patch. Amlexanox is indicated for the treatment of [ ] aphthous ulcers in adults and adolescents 12 years of age and older. OraDisc™ A should be applied to the ulcer as soon as possible after first noticing the symptoms of an aphthous ulcer and should be used four times daily, preferably following oral hygiene after breakfast, lunch, dinner, and [ ] before bedtime. In case of multiple ulcers, apply one patch to each ulcer. OraDisc™ A is supplied in bottles of 20 patches.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to Oradisc™ A to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[4]. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise

[1] MICROMEDEX Integrated Index, 2004, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-04, and the electronic online version of the FDA Orange Book.
[4] WWW location http://www.uspto.gov/tmdb/index.html.

was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name OraDisc A. Potential concerns regarding drug marketing and promotion related to the proposed name(s) were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name OraDisc A acceptable from a promotional perspective.

2. The Expert Panel identified four proprietary names that were thought to have the potential for confusion with OraDisc A. These products are listed in table 1 (see below), along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s), Established name	Usual adult dose*	Other**
OraDisc A	Amlexanox Mucoadhesive Patch 2 mg	One patch on each ulcer four times daily	
Oraqix	Lidocaine/Prilocaine Periodontal Gel 2.5%/2.5%	Use topically during dental procedures	SA
Orudis KT	Ketoprofen Tablets 12.5 mg	12.5 mg to 25 mg by mouth every 4 to 6 hours.	SA/LA
Oralone	Triamcinalone Acetonide Dental Paste 0.1%	Apply a small amount of paste to affected area two to three times daily	LA
Orabase	gelatin, pectin and sodium carboxymethylcellulose in Plastibase Paste	Apply a small amount of paste to affected area as needed.	LA

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)

B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to OraDisc A were discussed by the Expert Panel (EPD.

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of OraDisc A with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 123 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for OraDisc A (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: OraDisc A #20 QID ud	"The first prescription is for OraDisc A. Use 4 times a day as directed. Number 20..."
Inpatient RX: OraDisc A QID	

2. Results:

One respondent interpreted the proposed name as Orudis A. Orudis A sounds and looks similar to the currently marketed product Orudis KT.

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name OraDisc A, the primary concerns related to look-alike and sound-alike confusion with Orudis KT, Oralone, Orabase HCA, and Oraqix.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, one respondent from the verbal study misinterpreted the product as Orudis A, which sounds and looks similar to the currently marketed product, Orudis KT. The remaining misinterpretations were misspelled/phonetic variations of the proposed name, OraDisc A.

1. Sound-Alike and Look-Alike Concerns

   a. OraDisc A and Orudis KT can sound similar when pronounced and look similar when scripted. Orudis KT is a nonsteroidal anti-inflammatory agent indicated for temporary relief of minor aches and pains associated with common cold, headache, toothache, muscular aches, backache, minor arthritis pain, menstrual cramps, and reduction of fever. Since both products will only be available as OraDisc A and Orudis KT, the modifiers may be omitted by prescribers, thus the potential for sound-alike and look-alike confusion between OraDisc and Orudis is increased. This is possible since the modifiers do not provide any differentiating product characteristics. Timothy S. Lesar, PharmD conducted research at a 631-bed teaching hospital in order to evaluate prescribing errors involving medication dosage forms. Analysis of 402 medication errors that occurred over a 16-month period (Sept. 1999 – Dec. 2000) demonstrated that the most common error was due to the failure to specify a controlled-release dosage formulation through the use of a modifier (280 cases or 69.7%).[5] Studies such as this one support DMETS' concern that healthcare professionals my omit modifiers. OraDisc and Orudis both begin with the letters 'Or' and end with similar letters ('aDisc' vs. 'udis') which account for the orthographic and phonetic similarities of the names. Although the strengths are different, this may not help to distinguish the two products from each other. OraDisc and Orudis are only available in one strength; therefore the strength can be omitted from a prescription and still be dispensed because it is not required to verify a product selection. The two products also share the same frequency of administration (every 6 hours), overlap in route of administration (oral), and can overlap in quantity dispensed (20). Therefore prescriptions can be called in or written in a similar manner (e.g. "OraDisc, use as directed every 6 hours" vs. "Orudis, use as directed every 6 hours"). The sound-alike and look-alike characteristics, as well as the overlapping product characteristics increase the potential for medication errors between this name pair.

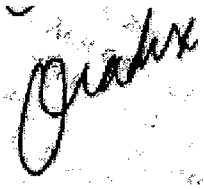
   b. OraDisc A can look similar to Oralone when scripted. Oralone is a corticosteroid used to treat the swelling and discomfort of the mouth and gums. OraDisc A is the only available dosage form of this product. Thus the modifier may be omitted by prescribers increasing the potential for look-alike confusion between OraDisc and Oralone. This is because the modifier 'A' does not provide any differentiating product characteristics. OraDisc and Oralone both begin with the same three letters, 'Ora,' which is the principal contribution to the look-alike characteristics of the names. Additionally, the endings of each name can look similar as well. The upstroke of the letter 'D' can resemble the letter 'l' especially if the letter 'D' is written in lower case. Furthermore, 'isc' can look similar to 'one,' depending on how it is scripted (see page 6). Since OraDisc and Oralone are only available in one strength, the strength can be omitted from a prescription and still be dispensed. Additionally, due to the nature of both products being used on an "as needed" basis for acute conditions and not used continuously for chronic conditions, it is not uncommon for the directions of the prescription to be "use as directed." Therefore it is possible to see prescriptions such as, "OraDisc, use as directed," or "Oralone, use as

[5] Lesar, Timothy S. Prescribing Errors involving Medication Dosage Forms. J Gen. Intern. Med.2002;17:579-87.

directed." Both products overlap in route of administration (oral) and will most likely be stored near each other on the pharmacy shelf. Therefore, the look-alike characteristics, along with the lack of distinguishing product characteristics, allow for an increased risk for medication errors due to name confusion.


c. OraDisc A can sound similar to Oraqix when pronounced. Oraqix is an anesthetic indicated for adults who require localized anesthesia in periodontal pockets during scaling and/or root planing. The beginnings of OraDisc A and Oraqix are identical ('Ora'), which is the principal contribution to the sound-alike similarities of the names. Additionally, the endings ('Disc' vs. 'qix') can sound similar. OraDisc A is the only dosage form of this product. Thus the modifier may be omitted by prescribers increasing the potential for look-alike confusion between OraDisc and Oralone. This is because the modifier 'A' does not provide any differentiating product characteristics. Although OraDisc and Oraqix have different dosage forms (mucoadhesive patch vs. periodontal gel), they will both be applied to the affected area of the mouth. Oraqix is intended to be used by dental professionals for use during dental procedures, and therefore, is generally not dispensed directly to patients. However, OraDisc A may be stocked in a dentist's office in addition to being available by prescription. The sound-alike similarities between OraDisc A and Oraqix and the conditions of use increase the potential for medication errors due to name confusion between OraDisc A and Oraqix.

d. OraDisc A can look similar to Orabase when scripted. Orabase is a plasticized hydrocarbon gel that is a component of several OTC products. Such products include Orabase B, Kenalog with Orabase, Orabase Baby Teething Gel, Orabase Lip Healing Gel, and Orabase with Benzocaine, and Orabase HCA. Orabase is a protective paste used to protect and soothe any sore and painful areas in the mouth or on the gums, including ulcers, sore spots from dentures, and toothbrush injury and to protect the skin around ileostomies, colostomies, fistulas and ileal conduits. OraDisc A is the only dosage form of this product. Thus the modifier may be omitted by prescribers increasing the potential for look-alike confusion between OraDisc and Oralone. This is because the modifier 'A' does not provide any differentiating product characteristics. OraDisc and Orabase both begin with 'Ora' and contain seven letters, which are the principal contributions to the look-alike characteristics of the names. Additionally, the upstrokes in each name ('d' vs. 'b') occur in the same position and can look similar depending on how they are scripted. In addition, the last two letters of the names ('sc' vs. 'se') can also look similar when scripted. Furthermore, both products would be applied to the affected areas of the mouth, several times a day (four times daily vs. as needed), while the condition being treated persists. While plain Orabase can be ordered alone, it is most often used in conjunction with another product such as Kenalog in Orabase, or Orabase with Benzocaine. If plain Orabase were prescribed, the pharmacist would have to call the prescriber and clarify the order to determine which product to dispense. Therefore, the necessity for the use of a modifier to correctly dispense Orabase helps to distinguish OraDisc A from Orabase enough to decrease the potential for medication errors due to name confusion.




2. Nomenclature Issues

Through further research on publicly accessible web sites, DMETS has learned that OraDisc is in fact a technology employing an erodible patch which adheres to the mucosal surface of the oral cavity for local drug delivery, or drug delivery to the systemic circulation. Additionally, the sponsor has already developed a benzocaine formulation using the OraDisc technology, which is listed on the website as OraDisc B. The standard practice for using names containing a technology or dosage from is to use the technology name or dosage form as a modifier (e.g. Zyprexa Zydis, Claritin Reditabs, Risperdal M-Tabs, etc.). It appears that the sponsor is doing the opposite, and using the technology name as the root name, and only using a single letter modifier ('A' or 'B') to indicate the active ingredient. Therefore, the same root name ('OraDisc') will be used for different active ingredients. This nomenclature practice could cause a proliferation of the name OraDisc in the marketplace, and may lead to confusion especially when the modifier that identifies the active ingredient is omitted or confused when scripted. Therefore, DMETS does not recommend the use of a technology as the root name of a product.

III. COMMENTS TO THE SPONSOR:

DMETS does not recommend the use of the proprietary name OraDisc A. In reviewing the proprietary name, the primary concerns related to look-alike and/or sound-alike confusion with Orudis KT. Include only the names that had the potential for confusion.

A. Look-Alike/Sound-Alike Issues

1. OraDisc A and Orudis KT can sound similar when pronounced and look similar when scripted. Orudis KT is a nonsteroidal anti-inflammatory agent indicated for temporary relief of minor aches and pains associated with common cold, headache, toothache, muscular aches, backache, minor arthritis pain, menstrual cramps, and reduction of fever. Since both products will only be available as OraDisc A and Orudis KT, the modifiers may be omitted by prescribers, thus the potential for sound-alike and look-alike confusion between OraDisc and Orudis is increased. This is possible since the modifiers do not provide any differentiating product characteristics. Timothy S. Lesar, PharmD conducted research at a 631-bed teaching hospital in order to evaluate prescribing errors involving medication dosage forms. Analysis of 402 medication errors that occurred over a 16-month period (Sept. 1999 – Dec. 2000) demonstrated that the most common error was due to the failure to specify a controlled-release dosage formulation through the use of a modifier (280 cases or 69.7%).[6] Studies such as this one support DMETS' concern that healthcare professionals my omit modifiers. OraDisc and Orudis both begin with the letters 'Or' and end with similar letters ('aDisc' vs. 'udis') which account for the orthographic and phonetic similarities of the names. Although the strengths are different, this may not help to distinguish the two products from each other. OraDisc and Orudis are only available in one strength; therefore the strength can be omitted from a prescription and still be dispensed because it is not required to verify a product selection. The two products also share the same frequency of administration (every 6 hours), overlap in route of administration (oral), and can overlap in quantity dispensed (20). Therefore prescriptions can be called in or written in a similar manner (e.g. "OraDisc, use as directed every 6 hours" vs. "Orudis, use as directed every 6 hours"). The

[6] Lesar, Timothy S. Prescribing Errors involving Medication Dosage Forms. J Gen. Intern. Med.2002;17:579-87.

sound-alike and look-alike characteristics, as well as the overlapping product characteristics increase the potential for medication errors between this name pair.

2. OraDisc A can look similar to Oralone when scripted. Oralone is a corticosteroid used to treat the swelling and discomfort of the mouth and gums. OraDisc A is the only available dosage form of this product. Thus the modifier may be omitted by prescribers increasing the potential for look-alike confusion between OraDisc and Oralone. This is because the modifier 'A' does not provide any differentiating product characteristics. OraDisc and Oralone both begin with the same three letters, 'Ora,' which is the principal contribution to the look-alike characteristics of the names. Additionally, the endings of each name can look similar as well. The upstroke of the letter 'D' can resemble the letter 'l' especially if the letter 'D' is written in lower case. Furthermore, 'isc' can look similar to 'one,' depending on how it is scripted (see page 6). Since OraDisc and Oralone are only available in one strength, the strength can be omitted from a prescription and still be dispensed. Additionally, due to the nature of both products being used on an "as needed" basis for acute conditions and not used continuously for chronic conditions, it is not uncommon for the directions of the prescription to be "use as directed." Therefore it is possible to see prescriptions such as, "OraDisc, use as directed," or "Oralone, use as directed." Both products overlap in route of administration (oral) and will most likely be stored near each other on the pharmacy shelf. Therefore, the look-alike characteristics, along with the lack of distinguishing product characteristics, allow for an increased risk for medication errors due to name confusion.

3. OraDisc A can sound similar to Oraqix when pronounced. Oraqix is an anesthetic indicated for adults who require localized anesthesia in periodontal pockets during scaling and/or root planing. The beginnings of OraDisc A and Oraqix are identical ('Ora'), which is the principal contribution to the sound-alike similarities of the names. Additionally, the endings ('Disc' vs. 'qix') can sound similar. OraDisc A is the only dosage form of this product. Thus the modifier may be omitted by prescribers increasing the potential for look-alike confusion between OraDisc and Oralone. This is because the modifier 'A' does not provide any differentiating product characteristics. Although OraDisc and Oraqix have different dosage forms (mucoadhesive patch vs. periodontal gel), they will both be applied to the affected area of the mouth. Oraqix is intended to be used by dental professionals for use during dental procedures, and therefore, is generally not dispensed directly to patients. However, OraDisc A may be stocked in a dentist's office in addition to being available by prescription. The sound-alike similarities between OraDisc A and Oraqix and the conditions of use increase the potential for medication errors due to name confusion between OraDisc A and Oraqix.

B. Nomenclature Issues

Through further research on publicly accessible web sites, DMETS has learned that OraDisc is in fact a technology employing an erodible patch which adheres to the mucosal surface of the oral cavity for local drug delivery, or drug delivery to the systemic circulation. Additionally, the sponsor has already developed a benzocaine formulation using the OraDisc technology, which is listed on the website as OraDisc B. The standard practice for using names containing a technology or dosage from is to use the technology name or dosage form as a modifier (e.g. Zyprexa Zydis, Claritin Reditabs, Risperdal M-Tabs, etc.). It appears that the sponsor is doing the opposite, and using the technology name as the root name, and only using a single letter modifier ('A' or 'B') to indicate the active ingredient. Therefore, the same root name ('OraDisc') will be used for different active ingredients. This nomenclature practice could cause a proliferation of the name OraDisc in the marketplace, and may lead to confusion especially when the modifier that identifies the active ingredient is omitted or confused when scripted. Therefore, DMETS does not recommend the use of a technology as the root name of a product.

C. Labeling, Packaging, and Safety Related Issues:

In the review of the container labels, carton and insert labeling of OraDisc A, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified the following areas of possible improvement, which might minimize potential user error.

1. CONTAINER LABEL

   a. Some of the letters (e.g. 'Di') in the proprietary name appear too close together (see below), making it difficult to read. Additionally, the different shades of boxing used around the name dissect the letter 'A' of 'Ora' in half, making the name difficult to read as well. Revise accordingly.

   b. Ensure the established name is at least one-half the size of the proprietary name.

2. INSERT LABELING

   a. General Comments

   Throughout the package insert, the medication is referred to in several different ways, (i.e. OraDisc A, Amlexanox OraDisc, and Amlexanox OraDisc A). Please use either the proprietary name (OraDisc A) or the established name (Amlexanox Patch) when referring to the medication in order to avoid confusion.

   b. PRECAUTIONS – Information for Patients Subsection

      i. Instruction Number 1:

         - Instruct patients to wash their hands before applying OraDisc A.

- Patients are instructed to apply OraDisc A [illegible] before bedtime in order to, "avoid the possibility of aspiration of soft, food-like particles that may come loose..." However, the patch may take up to 80 minutes to dissolve. Please advise patients to apply OraDisc A at least 80 minutes (e.g. an hour and a half) before bedtime, in order to allow time for the patch to completely dissolve.

ii. Instruction Number 2:

- Indicate up to how many patches may be used at one time.

iii. Instruction Number 3:

- Instruct patients what to do if the patch does not adhere readily.

iv. Instruction Number 5:

- Specify what is meant my particles in the statement, "...to ensure that no particles come loose during sleep."

- See second comment under Number 1.

c. The information provided in the Precautions section, Information for Patients, must be reprinted at the end of the labeling per CFR 201.57(f)(2). Revise accordingly.

Appears This Way
On Original

IV. RECOMMENDATIONS:

A. DMETS does not recommend the use of the proprietary name OraDisc™ A.

B. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review in order to minimize potential errors with the use of this product.

C. DDMAC finds the proprietary name OraDisc A acceptable from a promotional perspective.

D. DMETS recommends contacting Dr. Guirag Poochikian, Acting Chair of the CDER Labeling and Nomenclature Committee (LNC) regarding the established name of OraDisc™ A.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-2102.

Kristina C. Arnwine, PharmD
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Denise P. Toyer, PharmD
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

Attachment A

Inpatient Written	Outpatient Written	Verbal
Ora Disc A	CliaDisc A	Oradisc A
OraDisc	Ora Disc A	Oradisc A
Oradisc A	Ora Disc A	Oradisc A
OraDisc A	OraDisc A	Oradisc A
Oradisc A	Oradisc A	Oradisc A
OraDisc A	Oradisc A	OraDisc A
Oradisc A	OraDisc A	Oradisk A
Oradisc A	OraDisc A	Oradisk A
OraDisc A	OraDisc A	Oradisk A
Oradisc A	OraDisc A	Oradisk A
Oradisc A	OraDisc A	Oradisk A
Oradisc A	OraDisc A	OraDiskA
OraDisc A	OraDisc A	Oradisk-A
OraDisc A	Oradisc A	Orgis A
OraDisc A	Oradisc A	Orgis-A
Oradisc A	OraDisc A	Orudis-A
OraDisc A		
Oradisc A		
Oradisc A		
Oradix A		
OraDix A		

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Kristina Arnwine
8/13/04 03:00:00 PM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
8/13/04 03:22:38 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
8/13/04 03:34:23 PM
DRUG SAFETY OFFICE REVIEWER

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PHARMACEUTICALS, INC.

2600 Stemmons Freeway, Suite 176
Dallas, TX 75207-2107
Tel (214) 905-5100 Fax (214) 905-5101

www.accesspharma.com
e-mail: AKC@accesspharma.com

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MEGA/CDER

February 3, 2004

Jacquelyn Smith, Project Manager, Room N-236
Division of Dermatologic and Dental Drug Products, HFD-540
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

N-000(BZ)

ORIG AMENDMENT

Re: **OraDisc™A (Amlexanox 2mg, Mucoadhesive Patch)**
NDA No. **21-727**

Re: Submission of Clinical Study Protocols and Labeling in Word Format

Dear Ms. Smith:

As you requested, please find a desk copy on CD-ROM of the Amlexanox OraDisc clinical study protocols and draft labeling files in Word format. Included on this CD-ROM are:

- Study AP-C-1U106: Protocol and Amendment
- Study AP-C-1U107: Protocol and Amendments
- Study AP-C-2U108: Protocol
- Study AP-C-9E03: Protocol and Amendments
- Study AP-C-9E02: Protocol and Amendments
- Study AP-C-9E01: Protocol
- Study AP-C-9U05: Protocol and Amendment
- Draft Label
- Draft Insert.

If you have any questions, please contact me by phone at (214) 905-5100, by fax at (214) 905-5101, or by e-mail at alc@accesspharma.com.

Sincerely yours,

Amy Campbell

Amy Campbell
Manager, Regulatory Affairs

ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Director, Division of Medication Errors and Technical Support (DMETS), HFD-420
PKLN Rm. 6-34

FROM:
Jacquelyn Smith
Project Manager
Division of Dermatologic and Dental Drug Products

DATE: February 12, 2004	IND NO.	NDA NO. 21-727	TYPE OF DOCUMENT: New NDA	DATE OF DOCUMENT: December 4, 2003

NAME OF DRUG: OraDisc™ A (Amlexanox 2mg, Mucoadhesive Patch)	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG: 3S	DESIRED COMPLETION DATE: Labeling mtg. is July 19, 2004

NAME OF FIRM: Access Pharmaceuticals, Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- x☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

- ☐ CLINICAL
- ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

Please review the requested tradename "OraDiscTMA." The package insert and bottle label is attached. I will also send a hard copy. Labeling meeting is scheduled for July 19, 2004.

PDUFA DATE: October 8, 2004

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) x☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Division of Drug Risk Evaluation (DDRE), HFD-430 (Room 15B-08, PKLN Bldg.)			FROM: Jacquelyn Smith Project Manager Division of Dermatologic and Dental Drug Products	
DATE: February 12, 2004	IND NO.	NDA NO. 21-727	TYPE OF DOCUMENT New NDA	DATE OF DOCUMENT: December 4, 2003
NAME OF DRUG: OraDisc™ A (Amlexanox 2mg, Mucoadhesive Patch)	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG: 3S	DESIRED COMPLETION DATE: Labeling mtg. is July 19, 2004
NAME OF FIRM: Access Pharmaceuticals, Inc.				

REASON FOR REQUEST

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- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
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- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- x☐ OTHER *(SPECIFY BELOW)*:

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☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

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PDUFA DATE: October 8, 2004

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SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Division of Drug Marketing, Advertising and Communications, HFD-42
PKLN Room 17B04

FROM:
Jacquelyn Smith
Project Manager
Division of Dermatologic and Dental Drug Products

DATE: February 12, 2004	IND NO.	NDA NO. 21-727	TYPE OF DOCUMENT: New NDA	DATE OF DOCUMENT: December 4, 2003

NAME OF DRUG: OraDisc™ A (Amlexanox 2mg, Mucoadhesive Patch)	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG: 3S	DESIRED COMPLETION DATE: Labeling mtg. is July 19, 2004

NAME OF FIRM: Access Pharmaceuticals, Inc.

REASON FOR REQUEST

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- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE-NDA MEETING
- ☐ END OF PHASE II MEETING
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- ☐ PAPER NDA
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- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- x☐ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

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☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

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PDUFA DATE: October 8, 2004

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SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

4 Page(s) Withheld

_____ § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jacquelyn Smith
2/13/04 08:20:06 AM

ORIGINAL

ACCESS
PHARMACEUTICALS, INC.

2600 Stemmons Freeway, Suite 176
Dallas, TX 75207-2107
Tel (214) 905-5100 Fax (214) 905-5101

www.accesspharma.com
e-mail: AKC@accesspharma.com

N-000(BS)
ORIG AMENDMENT

January 30, 2004

RECEIVED
FEB 02 2004
CDR/CDER

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12,229 Wilkins Avenue
Rockville, MD 20852

RECEIVED
FEB 03 2004
MEGA/CDER

N-000- BS

Re: **OraDisc™A (Amlexanox 2mg, Mucoadhesive Patch)**
NDA No. **21-727**
Volume No. **3**

Re: Submission of SAS Datasets

Dear Sir or Madam:

Per the request of the DDDDP, please find the submission of SAS Datasets for studies AP-C-1U106 and AP-C-9E03 in the SAS transport format. Included on this CD-ROM are:

- Electronic copies of this cover letter and FDA From 356h in pdf format;
- Study AP-C-1U106: SAS dataset in SAS transport format; and
- Study AP-C-9E03: SAS dataset in SAS transport format.

If you have any questions, please contact me by phone at (214) 905-5100, by fax at (214) 905-5101, or by e-mail at alc@accesspharma.com.

Sincerely yours,

Amy Campbell

Amy Campbell
Manager, Regulatory Affairs

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Access Pharmaceuticals, Inc.	1/30/04
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(214) 905-5100	(214) 905-5101
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE**
2600 Stemmons Freeway, Suite 176 Dallas, TX 75207-2107	

RECEIVED
FEB 02 2004
CDR/CDER

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-727

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Amlexanox 2mg, Mucoadhesive Patch	OraDisc™A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
Amlexanox	

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Mucoadhesive Patch	2 mg	topical

RECEIVED
FEB 03 2004
MEGA/CDER

(PROPOSED) INDICATION(S) FOR USE:

Treatment of Aphthous Ulcers

ODUCT DESCRIPTION

PLICATION TYPE

(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

new dosage form for the treatment of aphthous ulcers

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See attached List

oss References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

D # 59,959: Amlexanox OraDisc
DMF #
DMF #
DMF #

Created by Media Arts/USDHHS: (301) 443-2454 EF

This application contains the following items: *(Check all that apply)*

☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* SAS data sets for pivotal studies

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
David Nowotnik	David P. Nowotnik, Ph.D.; Senior VP Research & Development	1-30-2004

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2600 Stemmons Freeway, Suite 176, Dallas, TX 75207-2107	(214) 905-5100

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CBER, HFM-94
12420 Parklawn Dr., Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

3.1 Form 356(h) Establishment Information

Company Name	Access Pharmaceuticals, Inc.
Address	2600 Stemmons Freeway
	Suite 176
	Dallas, TX 75207-2107
Contact	Ric Zarzycki, Ph.D. Director of Quality
Phone	(214) 905-5100
Activities at site	Finished product release testing, finished product stability testing
Inspection readiness	Ready for Inspection

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

Date: January 29, 2004

To: Amy Campbell, Manager, Regulatory Affairs	**From:** Jacquelyn Smith, Project Manager
Company: Access Pharmaceuticals, Inc.	Division of Dermatologic and Dental Drug Products
Fax number: (214) 905-5101	**Fax number:** (301) 827-2075
Phone number: (214) 905-5100	**Phone number:** (301) 827-2027
Subject: NDA 21-727/OraDisc™ A (Amlexanox 2mg, Mucoadhesive Patch) 012804 tcon	
Total no. of pages including cover: 5	

Document to be mailed: ☐ YES X NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 301-827-2020. Thank you.

MEMORANDUM OF TELECON

DATE: January 28, 2004, 12:30 PM

APPLICATION NUMBER: NDA 21-727

DRUG PRODUCT: OraDisc™ A (Amlexanox 2mg, Mucoadhesive Patch)

BETWEEN:

Name: David P. Nowotnik, Ph.D., Sr. Vice President, Research & Development,
Christiane M. Baud, Ph.D., Vice President, Clinical Development
Amy L. Campbell, Manager, Regulatory Affairs
[redacted] Biostatistics Consultant

Phone: (214) 905-5100
Representing: Access Pharmaceuticals, Inc.

AND

Name: Division of Dermatologic and Dental Drug Products, HFD-540
John V. Kelsey, DDS, M.B.A, Dental Team Leader
Mohamed Al-Osh, Ph.D., Team Leader, Biostatistics
Kathleen Fritsch, Ph.D., Biostatistician
Jacquelyn Smith, Regulatory Project Manager

SUBJECT: NDA 21-727

To facilitate the review process, the following information was requested by the Division.

1. Please submit the complete electronic database in SAS transport format for Study AP-C-1U106. The database must contain all efficacy, safety, and background data from the CRFs, including baseline data and data from each visit. Per the annotated CRF, the relevant files for Study AP-C-1U106 appear to be INCLUS, EXCLUS, DEMOG, MEDH, ORAL-EXM, EXAM, SBSM, CONMED, DIARY_M, DIARY-P, ADVE, AND DRGR. Each file needs to contain the treatment assignments. The efficacy data sets should also include derived values for all primary and secondary endpoints and any other variables needed to conduct the primary and secondary analyses, such as ulcer size, and success endpoints. The submitted files (pops.xpt and logit.xpt) are insufficient for review, as they do not contain all of the efficacy, safety, and background data. Also, the Agency cannot review Study AP-C-9E03 unless Access submits the electronic database for Study AP-C-9E03.

   Submit an official copy of the database to the NDA and a desk copy to Jacquelyn Smith before February 3, 2004.

2. Submit subgroup analysis results (tables and discussion) by gender, race, and age for the primary efficacy endpoints for Study AP-C-1U106. Submit the subgroup analyses to the NDA as soon as possible, but they may be submitted after February 9, 2004.

   The Sponsor agreed to submit the information officially and submit a desk copy to Jacquelyn Smith before February 3, 2004.

Appears This Way
On Original

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

John Kelsey
1/28/04 02:58:59 PM

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jacquelyn Smith
1/29/04 07:54:23 AM
CSO

ACCESS
PHARMACEUTICALS, INC.

2600 Stemmons Freeway, Suite 176
Dallas, TX 75207-2107
Tel (214) 905-5100 Fax (214) 905-5101

www.accesspharma.com
e-mail: AKC@accesspharma.com

January 8, 2004

N-000(C)

RECEIVED
JAN 12 2004
NEW CORRESP MEGA/CDER

Jonathan Wilkin, M.D., Director
Division of Dermatologic and Dental Drug Products, HFD-540
Food and Drug Administration
9201 Corporate Blvd.
Rockville, MD 20850

Re: **OraDisc™A (Amlexanox 2mg, Mucoadhesive Patch)**
NDA No. **21-727**
Volume No. **N/A - Correspondence**

Re: Corrected Cover Letter

Dear Dr. Wilkin:
The cover letter sent with the original submission of NDA 21-727, for Amlexanox 2mg, Mucoadhesive Patch, stated, in error, that the NDA was a 505(b)(2) submission. The letter should be corrected to read, as follows:

In accordance with 21 CFR 314.50, enclosed is an original 505(b)(1) New Drug Application for OraDisc™A (Amlexanox 2mg, Mucoadhesive Patch). The required user fee was submitted on December 5, 2003. A copy of the CTD Quality Information (Module 1, Module 2, and Module 3) is being sent concurrently to the FDA District Office in Dallas, TX.

The facilities for the production of the drug product, [ ] will be available for inspection in late January, 2004 or any date thereafter. The facilities for the production of the drug substance, [ ] are ready for inspection.

We appreciate the reviews and discussion by your staff during the IND stage of the development of the product. If you have any questions or additional comments, please contact me at (214) 905-5100 or at alc@accesspharma.com.

Sincerely yours,

Amy Campbell

Amy Campbell
Manager, Regulatory Affairs

ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING REVIEW LETTER

NDA 21-727

2/20/04

Access Pharmaceuticals, Inc.
Attention: David P. Nowotnik, Ph.D.
Senior VP, Research & Development
2600 Stemmons Freeway, Suite 176
Dallas, TX 75207-2107

Dear Dr. Nowotnik:

Please refer to your December 4, 2003, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for, OraDisc™ A (amlexanox) Mucoadhesive Patch, 2mg.

We also refer to your submissions dated December 12, 2003, January 8 and 30, 2004 and February 3, 2004.

We have completed our filing review, and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application has been filed under section 505(b) of the Act on February 6, 2004, in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues:

Chemistry, Manufacturing and Controls:

1. No environmental assessment or request for categorical exclusion has been provided.
2. We cannot locate data requested by the Division during the IND phase & pre-NDA meeting.
3. We cannot locate the Investigational Formulations information.
4. Desk copies of volumes 1.3, 1.4 and 1.5 to PHL-DO for the use of the inspector cannot be located and have been requested.

Clinical:

1. In Study AC-P-1U106, your reported results for the primary outcome variable show a statistically significant improvement on Day 5. However, at Day 7 this trend reversed.
2. In Study AC-P-1U106, the secondary endpoint, pain relief, shows no statistically significant improvement in the OraDisc at Day 5, or at any other day compared to vehicle patch.

Biostatistics:

1. There are no subgroup results of the primary efficacy endpoint by age (pediatric, adult, and geriatric), gender, race, baseline number of ulcers treated, baseline ulcer size, and baseline pain score for both intent-to-treat and efficacy evaluable populations.

We request that you submit the following information to address the potential review issues described above:

Chemistry, Manufacturing and Controls:

1. Please provide an environmental assessment or, if you intend to request a categorical exclusion, please provide the calculations to support the categorical exclusion.
2. Please identify where all data requested by the division during the IND phase & pre-NDA meeting can be found in the NDA.
3. Please indicate where the Investigational Formulations information can be found in the NDA.
4. Please forward desk copies of volumes 1.3, 1.4 and 1.5 to PHL-DO for the use of the inspector, as requested by telephone on February 17, 2004.

Clinical:

1. Please provide any explanation for why the trend for the primary outcome variable reverses on Day 7, with the vehicle patch showing a better outcome than the OraDisc.
2. Please provide any rationale for not seeing an improvement in pain scores.

Biostatistics:

1. For each of studies 1U106 and 9E03, please submit subgroup results of the primary efficacy endpoint by age (pediatric, adult, and geriatric), gender, race, baseline number of ulcers treated, baseline ulcer size, and baseline pain score for both intent-to-treat and efficacy evaluable populations.

Please respond to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call Jacquelyn Smith, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

Jonathan Wilkin, M.D.
Director
Division of Dermatologic and Dental Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Stanka Kukich
2/20/04 01:58:29 PM
Sign off for Dr. Jonathan Wilkin, Division Director

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

2/13/04

NDA 21-727

Access Pharmaceuticals, Inc.
Attention: Amy Campbell
Manager, Regulatory Affairs
2600 Stemmons Freeway
Suite 176
Dallas, TX 75207-2107

Dear Ms. Campbell:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: OraDisc (amlexanox) Mucoadhesive Patch, 2 mg

Review Priority: Standard (S)

Date of Application: December 4, 2003

Date of Receipt: December 9, 2003

Our Reference Number: NDA 21-727

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 6, 2003, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be October 9, 2004.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have submitted pediatric studies with this application. Once the review of this application is complete we will notify you whether you have fulfilled the pediatric study requirement for this application.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Dermatologic & Dental Drug Products, HFD-540
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Dermatologic & Dental Drug Products, HFD-540
9201 Corporate Boulevard
Rockville, Maryland 20850

If you have any questions, call Jacquelyn Smith, Regulatory Project Manager, at (301) 827-2020.

Sincerely,

{See appended electronic signature page}

MARY JEAN KOZMA-FORNARO
SUPERVISOR, PROJECT MANAGEMENT
Division of Dermatologic & Dental Drugs
Office of Drug Evaluation V
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jacquelyn Smith
2/13/04 11:40:47 AM
Signed for Mary Jean Kozma-Fornaro

NDA 21-727
N-000

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE 5

FACSIMILE TRANSMITTAL SHEET

Date: December 29, 2003

To: Amy Campbell, Manager, Regulatory Affairs	**From:** Jacquelyn Smith, Project Manager
Company: Access Pharmaceuticals, Inc.	Division of Dermatologic and Dental Drug Products
Fax number: (214) 905-5101	**Fax number:** (301) 827-2075
Phone number: (214) 905-5100	**Phone number:** (301) 827-2027

Subject: NDA 21-727/OraDisc™ A (Amlexanox 2mg, Mucoadhesive Patch) Original Submission

Total no. of pages including cover: 3

Document to be mailed: ☐ YES X NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at 301-827-2020. Thank you.

NDA 21-727
N-000

FDA Fax Memo

Date: December 29, 2003

Dear Ms. Campbell:

We are unable to locate records for the following facilities through the Office of Compliance:

- Access Pharmaceuticals, Inc., 2600 Stemmons Freeway, Suite 176, Dallas, TX 75207 [Finished Product Release Testing & stability testing]
- [redacted]
- [redacted]

Please confirm that these corporate names and addresses are correct and current. Copies of the most recent facilities registration form (FDA 2656) may be helpful in this respect.

Sincerely,

Jacquelyn Smith
Project Manager
DDDDP, HFD-540

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jacquelyn Smith
12/29/03 09:15:35 AM
CSO

ACCESS
PHARMACEUTICALS, INC.

2600 Stemmons Freeway, Suite 176
Dallas, TX 75207-2107
Tel (214) 905-5100 Fax (214) 905-5101

www.accesspharma.com
e-mail: AKC@accesspharma.com

RECEIVED
DEC 15 2003
CDR/CDER

December 12, 2003

RECEIVED
DEC 17 2003
MEGA/CDER

N-000(C)

NEW CORRESP

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12,229 Wilkins Avenue
Rockville, MD 20852

Re: **OraDisc™A (Amlexanox 2mg, Mucoadhesive Patch)**
NDA No. **21-727**
Volume No. **2**

Re: Resubmission of Electronic Files

Dear Sir or Madam:

As requested in your fax dated 12/11/2003, please find the resubmission of the electronic files in the correct electronic formats. Included on this CD-Rom are:

- Electronic copies of this cover letter and FDA From 356h in pdf format;
- Study AP-C-1U106: Annotated CRFs in pdf format, SAS dataset in SAS transport format, derived dataset specifications in pdf format;
- Study AP-C-9E03: Annotated CRFs in pdf format, SAS dataset in SAS transport format, derived dataset specifications in pdf format; and
- Bridging Analysis SAS transport format.

If you have any questions or comments, please contact me by phone at (214) 905-5100, by fax at (214) 905-5101, or by e-mail at alc@accesspharma.com.

Sincerely yours,

Amy Campbell

Amy Campbell
Manager, Regulatory Affairs

ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Access Pharmaceuticals, Inc.	12/12/03
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(214) 905-5100	(214) 905-5101
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
2600 Stemmons Freeway, Suite 176 Dallas, TX 75207-2107	RECEIVED DEC 15 2003 CDR/CDER

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-727

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
Amlexanox 2mg, Mucoadhesive Patch	OraDisc™A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*		CODE NAME *(If any)*
Amlexanox		
DOSAGE FORM:	**STRENGTHS:**	**ROUTE OF ADMINISTRATION:**
Mucoadhesive Patch	2 mg	topical

(PROPOSED) INDICATION(S) FOR USE:
atment of Aphthous Ulcers

RODUCT DESCRIPTION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
new dosage form for the treatment of aphthous ulcers

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See attached List

ORIGINAL

ss References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

ND # 59,959: Amlexanox OraDisc
DMF #
DMF #
DMF #

RECEIVED
DEC 17 2003
MEGA/CDER

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling *(check one)* ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☐	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☐	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* SAS data sets, electronic annotated CRFs

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
David Nowotnik	David P. Nowotnik, Ph.D.; Senior VP Research & Development	12/12/03

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2600 Stemmons Freeway, Suite 176, Dallas, TX 75207-2107	(214) 905-5100

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CBER, HFM-94
12420 Parklawn Dr., Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

2.1 Form 356(h) Establishment Information

Company Name	Access Pharmaceuticals, Inc.
Address	2600 Stemmons Freeway
	Suite 176
	Dallas, TX 75207-2107
Contact	Ric Zarzycki, Ph.D. Director of Quality
Phone	(214) 905-5100
Activities at site	Finished product release testing, finished product stability testing
Inspection readiness	Will be ready for inspection in mid-January, 2004

N-000

ACCESS
PHARMACEUTICALS, INC.

2600 Stemmons Freeway, Suite 176
Dallas, TX 75207-2107
Tel (214) 905-5100 Fax (214) 905-5101

www.accesspharma.com
e-mail: AKC@accesspharma.com

December 4, 2003

RECEIVED
DEC 0 9 2003
CDR/CDER

RECEIVED
DEC 1 2 2003
MEGA/CDER

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
12,229 Wilkins Avenue
Rockville, MD 20852

Re: OraDisc™A (Amlexanox 2mg, Mucoadhesive Patch)
NDA No. 21-727
Volume No. Original Submission

Dear Sir or Madam:

In accordance with 21 CFR 314.50, enclosed is an original 505(b)(2) New Drug Application for OraDisc™A (Amlexanox 2mg, Mucoadhesive Patch). The required user fee payment was submitted on December x, 2003. A copy of the CTD Quality Information (Module 1, Module 2, and Module 3) is being sent concurrently to the FDA District Office in Dallas, TX.

The facilities for the production of the drug product, [ ] will be available for inspection in late January, 2004 or any date thereafter. The facilities for the production of the drug substance, [ ]

We appreciate the reviews and discussion by your staff during the IND stage of the development of the product. If you have any questions or additional comments, please contact me at (214) 905-5100 or at alc@accesspharma.com.

Sincerely yours,

Amy Campbell

Amy Campbell
Manager, Regulatory Affairs

ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER
21-727

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Access Pharmaceuticals, Inc.	12/4/03
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE** *(FAX)* **Number** *(Include Area Code)*
(214) 905-5100	(214) 905-5101
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* **IF APPLICABLE**
2600 Stemmons Freeway, Suite 176 Dallas, TX 75207-2107	RECEIVED DEC 09 2003 CDR/CDER

RECEIVED
DEC 12 2003
MEGA/CDER

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-727

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY	
Amlexanox 2mg, Mucoadhesive Patch	OraDiscTMA	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*		**CODE NAME** *(If any)*
Amlexanox		
DOSAGE FORM:	**STRENGTHS:**	**ROUTE OF ADMINISTRATION:**
Mucoadhesive Patch	2 mg	topical

(PROPOSED) INDICATION(S) FOR USE:
tment of Aphthous Ulcers

DUCT DESCRIPTION

APPLICATION TYPE *(check one)* ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

Name of Drug _____ Holder of Approved Application _____

TYPE OF SUBMISSION *(check one)* ☒ ORIGINAL APPLICATION ☐ AMENDMENT TO APENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
new dosage form for the treatment of aphthous ulcers

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 43 THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

See attached List

ORIGINAL

References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND # 59,959: Amlexanox OraDisc
DMF #
DMF #
DMF #

This application contains the following items: *(Check all that apply)*	
☒	1. Index
☒	2. Labeling *(check one)* ☒ Draft Labeling ☐ Final Printed Labeling
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☒	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
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☐	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
☒	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
☒	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
☒	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
☒	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601.2)
☒	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or (j)(2)(A))
☒	15. Establishment description (21 CFR Part 600, if applicable)
☒	16. Debarment certification (FD&C Act 306 (k)(1))
☒	17. Field copy certification (21 CFR 314.50 (l)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☒	19. Financial Information (21 CFR Part 54)
☐	20. OTHER *(Specify)*

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE:
David Nowotnik	David P. Nowotnik, Ph.D.; Senior VP Research & Development	12/4/03

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
2600 Stemmons Freeway, Suite 176, Dallas, TX 75207-2107	(214) 905-5100

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

ment of Health and Human Services
and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CBER, HFM-94
12420 Parklawn Dr., Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

1.1 Form 356(h) Establishment Information

Company Name	Access Pharmaceuticals, Inc.
Address	2600 Stemmons Freeway
	Suite 176
	Dallas, TX 75207-2107
Contact	Ric Zarzycki, Ph.D. Director of Quality
Phone	(214) 905-5100
Activities at site	Finished product release testing, finished product stability testing
Inspection readiness	Will be ready for inspection in mid-January, 2004

MEMORANDUM OF TELECON

DATE: November 7, 2003, 2:00 PM

APPLICATION NUMBER: IND 59,949

DRUG PRODUCT: Amlexanox OraDisc

BETWEEN:

Name: David P. Nowotnik, Ph.D., Sr. Vice President, Research & Development,
Christiane M. Baud, Ph.D., Vice President, Clinical Development
Ric Zarzycki, Ph.D., Director, Quality Control and Logistics
Amy L. Campbell, Manager, Regulatory Affairs

Phone: 214-905-5100
Representing: Access Pharmaceuticals, Inc.

AND

Name: Division of Dermatologic and Dental Drug Products, HFD-540
Mary Jean Kozma-Fornaro, Chief, Project Management Staff
Jacquelyn Smith, Regulatory Project Manager

SUBJECT: IND 59,949

The teleconference was requested by the Agency to discuss IND 59,949, Amlexanox OraDisc, in regard to the October 20, 2003 submission stating the Sponsor's opinion of having met the criteria required for a submission based upon a single pivotal study. In the August 13, 2003, the Agency felt that the requirement of very persuasive statistical findings for a single study did not appear to have been met. In the October 20, 2003 submission, the Sponsor provided several options, the Early and Final formulations, line extension and filing as a 505(b)(2) and wanted the Agency's advice on these options.

The Sponsor felt that the October 20, 2003 submission would save time and get feedback on a viable option.

The Agency expressed that it is the Sponsor's responsibility to decide on an option.

The Sponsor noted the Agency's position on the option decision being their responsibility.

The conversation ended amicably.

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/s/

Mary Jean Kozma Fornaro
12/9/03 10:09:33 AM

MEMORANDUM OF MEETING MINUTES

Meeting Date: August 13, 2003 **Time:** 1:00 PM

Location: N225

Application: IND 59, 949, Amlexanox OraDisc
Guidance Meeting

Meeting ID: 11016

Sponsor: Access Pharmaceuticals, Inc.

Meeting Chair: Jonathan Wilkin, M.D., Director, DDDDP, HFD-540

Meeting Recorder: Jacquelyn Smith, Project Manager, DDDDP, HFD-540

FDA Attendees, Titles, and Office/Division:

Jonathan Wilkin, M.D., Division Director, DDDDP, HFD-540
John V. Kelsey, DDS, M.B.A, Dental Team Leader, DDDDP, HFD-540
Frederick Hyman, DDS, M.P.H., Dental Officer, DDDDP, HFD-540
Norman See, Ph.D., Pharmacology Reviewer, DDDDP, HFD-540
Chandra Chaurasia, Pharm.D., Pharmacokinetics, DPEIII, HFD-880
Mohamed Al-Osh, Ph.D., Team Leader, Biostatistics, DBIII, HFD-725
Steven Thomson, Ph.D., Biostatistian, DBIII, HFD-725
Wilson DeCamp, Ph.D., Team Leader, Chemistry, DNDCIII, HFD-830
Ernest Pappas, Chemistry Reviewer, DNDCIII, HFD-830
Jonca Bull, M.D., Director, ODE V, HFD-105
Terri Rumble, R.N., B.S.N/Associate Director of Regulatory Affairs, ODE V, HFD-105
Brian Harvey, M.D., Deputy Director, ODE V, HFD-105
Leonthena Carrington, Project Manager, DDDDP, HFD-540
Virginia Giroux, Project Manager, DDDDP, HFD-540
Millie Wright, Project Manager, DDDDP, HFD-540
Jacquelyn Smith Project Manager, DDDDP, HFD-540

External Constituent Attendees and Titles:

David P. Nowotnik, Ph.D., Sr. Vice President, Research & Development, Access Pharmaceuticals, Inc.
Christiane M. Baud, Ph.D., Vice President, Clinical Development, Access Pharmaceuticals, Inc.
Amy L. Campbell, Manager, Regulatory Affairs, Access Pharmaceuticals, Inc.
[redacted], Biostatistics Consultant
[redacted] Medical Consultant (via teleconference)

Purpose:

To provide general guidance on the content and format of the Investigational New Drug Application under 21CFR 312. The pre-meeting briefing document provides background and questions for discussion.

Chemistry, Manufacturing and Controls:

This meeting package contained a list of specific questions regarding CMCs. However, it is noted that the Sponsor did not address all of the CMC issues conveyed to them during the EOP-2 meeting of 8/20/01 and in the meeting minutes of 11/02/01. Some of the CMC issues were mentioned in the proposed meeting package. It is also noted that the Sponsor's amendment of 4/5/03 contained some of the information as requested; however, they did not indicate if this information was in response of the meeting minutes of 11/02/01. The Sponsor should indicate if all of the CMC issues have been addressed and where to find this information. This should be done before the NDA is submitted.

The sponsor stated that they were aware that they may not have responded to all issues raised at the EOP2 meeting. Certain responses appeared in amendment N-014. They will submit a summary of responses to all the issues.

Sponsor's Question # 1
Access will summarize information from Aphthasol® (amlexanox oral paste) 5%, NDA# 20-511 for chemistry, manufacturing, and controls information on the amlexanox drug substance and reference the NDA for individual documents and supporting data. Only new information on the stability of the drug substance not included in the NDA 20-511 will be provided in the Amlexanox OraDisc™ mucoadhesive patch submission. Does the Agency concur with this proposal?

Agency's Response:
The answer is yes, providing that the new stability information is also submitted to NDA holder of NDA 20-511.

In addition, even though "amlexanox mucoadhesive patch" was recommended during the EOP-2 meeting as a dosage form description, the Office of Drug Safety will have to approve this term, and may not approve it. This dosage form is not recognized in the CDER Data Standards Manual. We recommend that you consider an alternate such as [

]

Sponsor's Question # 2
Access proposes that the following tests are sufficient for the regulatory QC release of Amlexanox OraDisc™ mucoadhesive patch:

- [
-
-
-
-

]

The test methods listed above will be provided in the briefing document. Are these methods acceptable to the agency, and meet the criteria for regulatory QC release testing?

Agency's Response:
As proposed in the meeting package, they appear to be acceptable. However, this does not rule out the possibility that additional information may be required following our review of the data. Therefore, this will be answered at the time of the NDA review.

Because of concerns that amlexanox [ ] the mucoadhesive layer, please consider expanding the appearance quality attribute to include a test for [ ] when the mucoadhesive layer is exposed. This should be included in both release and stability testing. FDA clarified that the previous request for [ ] (at the EOP2 meeting) had been reconsidered, and that dissolution would suffice for this purpose.

The sponsor stated that amlexanox was [ ] in the mucoadhesive layer, not dissolved. FDA acknowledged this, and noted that the appearance test was too subjective. A microscopic examination of the mucoadhesive layer [ ] may be needed.

Sponsor's Question # 3
Access will propose an expiry term of 12 months based on the stability data generated from three clinical batches. The stability data will be presented in the briefing package. Does the Agency concur with the proposed expiry term?

Agency's Response:
The data submitted in the briefing are sufficient (3 lots, 12 months at room temperature) to support an expiration date of 12 months. It is not clear if these lots are in the to-be-marketed package. Any additional data submitted with the NDA will be reviewed in support of your proposed expiry. Additional data may support a longer shelf life.

Pharmacology/Toxicology:

Sponsor's Question # 4
A complete set of nonclinical studies for oral administration of amlexanox formulated as tablets and as a paste has been completed and was included in the Aphthasol NDA # 20-5-11. Access will format the pharmacology, pharmacokinetics, and toxicology summaries (written and tabulated) from NDA 20-511 including any new information, but will not include study reports from NDA 20-511. However, any data/publications on other formulations not included in NDA 20-511 will be included in their entirety in the Amlexanox OraDisc™ mucoadhesive patch submission. Does the Agency find this acceptable?

Agency's Response:
Yes.

Biopharmaceutics:

Sponsor's Question # 5
Access would like to request a waiver of the requirement for the submission of evidence *in vivo* bioavailability according to 21 CFR 320.22. The drug product is a topically applied preparation intended for local therapeutic effect, an exemption allowed by 21 CFR 320.22(b)(2). Does the Agency concur?

Agency's Response:
No, the Agency does not concur. 21 CFR 320.22 (b)(2) reads as follows:

b. For certain drug products, the in vivo bioavailability or bioequivalence of the drug product may be self-evident. FDA shall waive the requirement for the submission of evidence obtained in vivo measuring the bioavailability or demonstrating the bioequivalence of these drug products. A drug

product's in vivo bioavailability or bioequivalence may be considered self-evident based on other data in the application if the product meets one of the following criteria:

(1) N.A.

(2) The drug product:

(i) Is administered by inhalation as a gas, e.g., a medicinal or an inhalation anesthetic; and

(ii) Contains an active ingredient in the same dosage form as a drug product that is the subject of an approved full new drug application or abbreviated new drug application.

As your product is not administered by inhalation, it does not qualify under this section of the waiver provisions.

Sponsor's Question # 6
Access has conducted a single-dose pharmacokinetic study in which 18 subjects received one, two or three Amlexanox OraDisc™ mucoadhesive patches, and as part of the Phase 3 study, has determined the serum levels of amlexanox pre-dose and 2 hr post-dose on Day 4 of multiple dosing with Amlexanox OraDisc mucoadhesive patches in 31 patients. A summary of the results will be in the briefing package. Access will submit the (1) pharmacokinetic study and (2) the data from the Phase 3 study as the complete pharmacokinetic data package to support the NDA submission? Does the Agency find this acceptable?

Agency's Response:
The Agency recommends that each multiple dose study should include enough subjects to obtain a meaningful pharmacokinetic profile of the drug in question. It is noted that the Agency had made the following comments in its response dated March 28, 2002 to the Protocol review (IND 59,949, submission date: Dec. 26, 2001):

"The sponsor needs to clarify how they want to extrapolate data from a single dose study to multiple dose situation."

Also, pharmacokinetic profile under maximal use conditions in accordance to the proposed labeling is requested.

Sponsor's Question # 7
Access plans to include four clinical studies conducted with the Early formulation OraDisc product. In one of the studies the serum level of amlexanox pre-dose and 1 hr post-dose on Day 4 of multiple dosing with the first generation OraDisc product was measured in 55 patients. These data have been previously submitted to the IND, and a summary of the results will be included in the briefing package. Access will submit these results as supportive pharmacokinetic data for the current Amlexanox OraDisc™ mucoadhesive patch pharmacokinetic data package. Does the Agency find this acceptable?

Agency's Response:
Yes. However, it is noted that these studies will provide only indirect supportive data, and may not

Additional Biopharmaceutics Comment:

We note that no studies have been conducted to assess the impact of food on the bioavailability/retention of the amlexanox OraDisc. In lieu of such information the Sponsor should recommend that the product be applied [ ] to ensure adhesion and proper drug release.

Clinical and Biostatistics:

Sponsor's Question # 8

Access has conducted a Phase 3 clinical trial including 701 patients with minor aphthous ulcers. The study report has been completed and will be submitted to the IND. A summary of the results will be provided in the briefing document. Access considers this study to be of sufficient quality to qualify as a single "very persuasive study" (from minutes of August 20, 2001 End-of-Phase 2 Meeting) in support of the submission. Does the Agency concur with this opinion?

Agency's Response:

The acceptability of the study to support drug approval would be a review issue. However, based on the analysis that you provide in the submission, your results do not appear to be "very persuasive." Based on that assessment, the Agency has reclassified this as a Guidance Meeting.

At this point, you could [ ]

].

Another option would be to compare the OraDisc to the marketed formulation of Amlexanox (Aphthasol) – this would be a line extension. Whatever you decide to do, you are encouraged to come in for a meeting to get agreement with the Agency prior to conducting the study.

Discussion at the Meeting: The Sponsor expressed surprise that the Division did not consider the results of the completed study of the final formulation "very persuasive." They noted that they had accepted the Division's suggestion that they enroll patients with multiple aphthae in their study. They also noted that the Guidance Document, "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products," does not specify what level of statistical significance is considered very persuasive. The Division responded that even though the guidance doesn't specify a level of significance, it can be assumed that it would be a higher magnitude than that for statistical significance in a study that is to be one of two. In addition, the acceptability of the p-value would be impacted by other factors like the magnitude of the treatment effect. The statistical consultant for the Sponsor asked why the Division had not pointed out that the proposed study was not powered to achieve "very persuasive" statistical significance. The Division responded that the Sponsor had not said that this was to be a single-study submission and had not asked whether the study was powered for that situation. (Addendum: Following this meeting a review of the record was conducted. The Division is unable to find a statement by the Sponsor in the request for Special Protocol Assessment in which they say that they intend to seek approval based on a single study.)

A second line of discussion concerned whether there was a need for another study to support efficacy, since the "Early formulation" of the disc was similar to the to-be-marketed product and because another formulation of amlexanox is already marketed. The Sponsor argued that studies conducted with these other formulations should provide the necessary supportive evidence. The Division responded that even seemingly minor changes in formulation may affect the efficacy of a product, and studies in other formulations could not be considered pivotal.

Addendum (Response to the sponsor fax dated August 18, 2003):

The Sponsor, in their submission of August 18, 2003, reiterated their view that the results of the statistical analyses for Study AP-C-1U106 constitute very persuasive statistical findings, one of the requirements for a single study submission. In response, it should be noted that according to the study protocol, efficacy evaluation would start by testing the hypothesis that no overall treatment effect among the three treatment arms (amlexanox, vehicle and no treatment) using the Cochran-Mantel-Haenszel (CMH) test, and if this is significant then the amlexanox versus vehicle comparison would be tested using the CMH test as the primary analysis and using the logistic regression as a secondary analysis.

The sponsor's summary of the efficacy results of Study AP-C-1U106 shows that the p-value for the overall test for the percentage of subjects with all treated ulcers healed at Day 5 is 0.031 and the p-value for the primary analysis for testing amlexanox versus vehicle is 0.015. It should be noted that the highly significant p-value for testing amlexanox versus vehicle (p-value = 0.007) was based on fitting the logistic regression model. It is impossible to make judgements about the reported p-value without checking the fitted model, however, we note that logistic regression is specified as a secondary analysis in the protocol.

The Agency continues to feel that the requirement of very persuasive statistical findings for a single study submission do not appear to have been met. In addition to a very small p-value, the magnitude of treatment effect compared to the vehicle, and internal consistency of efficacy results across study and subgroups also impact on the persuasiveness of the study. The sponsor is again referred to the Guidance, "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products."

Sponsor's Question # 9
Access plans to include four clinical studies conducted with the Early formulation OraDisc product. Data for these studies have been previously submitted to the IND, and a summary of the results will be provided in the briefing package. These studies will be pooled in a comprehensive database used to evaluate clinical safety in patients. Does the Agency agree that data from the Early formulation OraDisc product can be added to the safety database?

Agency's Response:
If you were to submit the NDA at this time, the Agency would like to have the safety data on the Early formulation submitted in the NDA, but it should be separate from the safety data on the Final formulation.

Sponsor's Question # 10
Access plans to include four clinical studies conducted with the Early formulation OraDisc. A summary of the results will be provided in the briefing package. These studies will be included as supportive data for the efficacy of the Final formulation. Does the Agency agree that these data can be used as supportive data for efficacy of the current Amlexanox OraDisc™ mucoadhesive patch?
Agency's Response:
If you were to submit the NDA at this time, the utility of the data on the Early formulation would be a review issue.

Sponsor's Question # 11
Access has conducted clinical studies that included a total of 128 pediatric patients (67 on active) and compiled a pediatric database. A summary of the safety results will be provided in the briefing package. Access considers the data to be of sufficient quality to support a pediatric indication. Does the Agency concur?

Agency's Response:
The utility of the pediatric data to support a pediatric indication would be a review issue.

Sponsor's Question # 12
Access plans to submit the Amlexanox OraDisc NDA in the paper CTD format. Does the Agency find this acceptable?

Agency's Response:
Yes. The Agency's contact person for CTD submissions is Gary Gensinger: (301) 827-7753.

Sponsor's Question # 13
In order to facilitate review of the NDA, Access will submit portions of the submission in electronic format in addition to the paper CTD. Access plans to prepare a folder system with documents saved in Adobe Acrobat format without hyperlinks. Our clinical safety and efficacy databases will be submitting in SAS datasets. Does the Agency find these formats acceptable for electronic submission?

Agency's Response:
Yes. The Agency would like to have a paper copy of the summary of the NDA (Vol.1) to facilitate supervision of the review. We would also request annotated case report forms indicating variable names and resident dataset for each variable. Algorithms for derived variables should also be included.

For additional information, please refer to the guidance, Providing Regulatory Submissions in Electronic Format-NDAs, http://www.fda.gov/cder/ guidance/2353fnl.pdf. The contact person is Gary Gensinger: (301) 827-7753.

Sponsor's Question # 14
Access plans to place the clinical studies conducted with the first-generation OraDisc product in Module 5, Section 5.3.5.4 (Efficacy and Safety Studies) Other Study Reports. Does the Agency agree that this section is the appropriate place for these data?

Agency's Response:
If you were to submit the NDA at this time, this is an acceptable place to report the data from the studies using the Early formulation, but the utility of the data from these studies remains a review issue.

Project Management:

1. For applications submitted after February 2, 1999, per 21CFR 54.3 and 21CFR 54.4, an NDA applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests.

2. Comments shared today with the Sponsor are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of the information submitted to the NDA might identify additional comments or informational requests.

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/s/

Jonathan Wilkin
9/12/03 01:16:11 PM

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/s/

Jacquelyn Smith
9/12/03 01:26:24 PM
CSO

MEMORANDUM OF MEETING MINUTES

Meeting Date:	August 20, 2001	Time: 1:00 PM
Location:	9201 Corporate	S 400
Application:	IND 59,949	End-of-Phase 2
Meeting ID:	7294	
Sponsor:	Access Pharmaceuticals, Inc.	
Meeting Chair:	Jonathan Wilkin, M.D./Division Director	
Meeting Recorder:	Victoria Lutwak/Project Manager	

FDA Attendees, Titles, and Office/Division:

Jonathan Wilkin, M.D./Division Director, DDDDP, HFD-540
Jonca Bull, M.D./Acting Director, ODE V, HFD-105
Bonnie Dunn, Ph.D., Deputy Director, ONDC/DNDCIII, HFD-830
Wilson DeCamp, Ph.D./Team Leader, Chemistry, DNDCIII, HFD-830
Ernest Pappas/Chemistry Reviewer, DNDCIII, HFD-540
Abigail Jacobs, Ph.D./Supervisor, Pharmacology DDDDP, HFD-540
Dennis Bashaw, Pharm.D./Team Leader, Pharmacokinetics, DPEIII, HFD-880
John Kelsey, D.D.S., M.B.A./Team Leader, Dental, DDDDP, HFD-540
Clarence C. Gilkes, D.D.S./Dental Reviewer, DDDDP, HFD-540
Mohamed Alosh, Ph.D./Team Leader, Biostatistics DBIII, HFD-725
Kathleen Fritsch, Ph.D./Biostatistian, DBIII, HFD-725
Victoria Lutwak/Regulatory Project Manager, DDDDP, HFD-540

External Constituent Attendees and Titles:

Access Pharmaceuticals, Inc.
David P. Nowotnik, Ph.D., Vice President, Research & Development
Daniel G. Moro, Sr. Director, Drug Delivery
Christiane M. Baud, Ph.D., Sr. Director, Clinical Development
Amy L. Campbell, Manager, Regulatory Affairs Consultants
Martha R. Charney, Ph.D., Regulatory Consultant
[ ] Toxicology Consultant
[ ] Biostatistics
[ ] Medical Consultant by telephone conferencing

Purpose:

The objectives for this End-of-Phases 2 meeting are to discuss the testing required for a formulation change, the results of the preclinical studies; and to confirm agreement on the remaining preclinical work; and to reach agreement on the proposed Phase 3 clinical protocol. Amlexanox OraDisc, 2 mg, is indicated for the treatment of recurrent minor aphthous ulcers.

Chemistry, Manufacturing and Controls:

Sponsor's Question # 1: The Sponsor will modify the formulation of OraDisc™ . Details of the formulation are provided in the Chemistry Manufacturing and Controls Section of this document. The Sponsor proposes that the old and new formulations are sufficiently similar to allow for use of data from our recently completed Phase 2/3 clinical study in the NDA. The Sponsor wishes to know whether the Agency concurs with this proposal?

FDA Response: The answer is no, these formulations are not similar. The new excipients in the backing give added assurance of the rate of erosion of the wafer in the mouths. However, the mucoadhesive layer is significantly different, especially with regard to the concentration of amlexanox, [ ] in the new formulation, although the amount per patch remains the same.

The chemist has the following requests:

1. The excipient, [ ] is a trade name designation and should be identified by its chemical name. If it is a novel excipient, never used in a US approved product, a DMF or equivalent information, should be provided to the IND.
2. Under item B. (pg. 19)- Name and Address of Manufacturer for backing layer, please indicate if more than one manufacturing site is used.

Sponsor's Question # 2: A dissolution test method and preliminary test results for Amlexanox OraDisc™ are provided in the CMC Section of this document. The Sponsor wishes to know whether this method is acceptable to the agency, and meets the criteria described by the Agency at the pre-I ND meeting on November I 0, 1999.

FDA Response: The answer is yes. However, the [ ] speed [ ] seems high - is this an error?

[ ]

Sponsor's Question # 3: A [ ] test method for Amlexanox OraDisc™ is provided in the CMC Section of this document. The Sponsor will compare the old OraDisc™ formulation with the new formulation. The Sponsor does not plan to conduct any other types of *in vitro* tests. Does the Agency concur?

FDA Response: [ ]
however; this drug product does not meet that criterion.

Sponsor's Question # 4: The Sponsor proposes the [ ] for the dosage form. Does the Agency concur?

FDA Response: The answer is no. We refer you to the CDER Data Standards Manual. It should be described as "amlexanox mucoadhesive patch." Please address in labeling accordingly.

Additional Comments:

1. The stability statement on page 24 of the meeting package is ambiguous in that it does not include a stability protocol. Please clarify.

During our pre-IND meeting on November 11, 1999, we recommended that, during the Phase 3 studies, stability data should be obtained on three (3) batches, using an acceptable stability protocol, which should be promptly submitted to the IND. The primary batches should be of the same formulation and packaged in the same container/closure system as proposed for marketing to simulate production batch. Two of the three batches should be at least pilot scale batches and the third one can be a smaller scale production batch, provided that the manufacturing process meaningfully simulates that which would be used for large scale batches for marketing. Reduced requirements for the submission of stability data are described in ICH Q1c "Stability Testing for New Dosage Forms," available on our Internet site. We recommend that you consult this and related guidances to determine the appropriate length of your stability studies for your planned NDA submission.

2. [ ]

3. Where appropriate, [ ] should be described in the bulk as an in-process control during the manufacture of the amlexanox film.

4. We recommend that you assure yourselves that all manufacturing sites for Amlexanox OraDisc are ready for inspection at the time of the NDA submission.

Pharmacology/Toxicology:

Sponsor's Question #5 A complete set of toxicological studies for oral administration of amlexanox...is included in NDA 20-511. In addition, amlexanox has been tested in a mouse lymphoma assay. The sponsor believes that the non-clinical database is sufficient to support an NDA for Amlexanox OraDisc, 2mg, without the generation of additional toxicological data. Does the agency concur?"

FDA Response: The database appears to be adequate to support filing of a NDA with respect to the safety of amlexanox. Please note that the NDA should contain appropriate data to support the proposed exposure to each excipient in the product, as well as any impurities that may be present. In particular, it is unclear if the excipients [ ]' are adequately qualified. They are present in the new formulation [ ] and the product would be orally administered to healthy individuals on a chronic basis. Unless the sponsor can document that a given excipient is qualified under the proposed conditions of exposure (e.g., GRAS as a direct food additive, present in a drug product that is approved for chronic oral administration to essentially healthy individuals, etc.), then data needed to support the proposed exposure to that excipient may include chronic toxicology data, reproductive toxicology data, genetic toxicology data, and carcinogenicity data. It is recommended that the sponsor submit an amendment to the IND in the near future that discusses each excipient and explains why the sponsor believes it is (or will be) qualified within the context of an NDA.

The NDA should explain why the drug product or backing material would not be aspirated (including while a patient was asleep), and why the potential to induce choking is not an issue.

Biopharmaceutics:

We concur with the reviewing FDA chemist in that use of [ ] test is not warranted by the data supplied by the sponsor in this package. As for their in vitro dissolution, the method as proposed uses a [ ] We feel this is an excessive speed and would

like to see dissolution results using more traditional speeds as outlined in the USP and in FDA guidance documents.

From discussions with the sponsor during the meeting it was learned that the recently conducted phase 2/3 trial did in fact use the old formulation. As the Agency considers the old and new formulations to be different, a new in vivo trial will be required. As to the related issue of bridging of the clinical data, evaluation of the erratic nature of amelexanox plasma levels suggest that in vivo biotesting is not likely to be successful in establishing bioequivalence. In lieu of pk linkage the sponsor was advised to consider an in vivo clinical trial to establish the equivalence of these two formulations.

Clinical:

Sponsor's Question #7: The Sponsor has conducted a Phase 2/3 clinical trial including 401 patients with minor aphthous ulcers using the old formulation. The study report has been completed and submitted to the IND. A summary of the results is provided in the Clinical Report Summary section of this document. The Sponsor considers this study to be of sufficient quality to qualify as one of the pivotal studies. Does the Agency concur?

FDA Response: The Agency does not consider the two formulations of OraDisc™ to be sufficiently similar to allow the data from the completed study to be used as pivotal for approval of the new formulation. The Sponsor [ ] In addition, the Division makes commitments regarding study design at the End-of-Phase 2 meeting. Because you declined to have an EOP2 meeting, you don't have benefit of commitments regarding the completed study. The utility of the completed study in supporting an NDA submission will be a review issue. Given the information available about other formulations of amlexanox, the Agency might be willing to accept a single study to support filing of an NDA, but it would have to a very persuasive study, with robust results and no significant flaws. The Sponsor is referred to FDA's "Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products," for discussion of the issue.

Sponsor's Question #8: The Sponsor proposes to conduct a pivotal trial of amlexanox OraDisc™ (new formulation) versus vehicle disc and no treatment. The design and statistical analyses will be identical to those of the recently completed Phase 2/3 trial. An outline of the proposed pivotal trial and statistical hypothesis is provided in this document. Does the Agency concur? (The Sponsor submitted the complete protocol as Serial 011.)

FDA Response: The Division has the following comments about the proposed Phase 3 study:

1. The inclusion of pediatric patients only down to age 12 seems reasonable, given the potential difficulty of applying and maintaining the dosage form in the mouth, but the lower end of the age range should be significantly represented.

2. The Sponsor does not state whether adverse event information will be solicited from the patient, or simply reported if the patient spontaneously provides the information. There should be a system for actively soliciting such reports, perhaps including a script. A question regarding aspiration or other problems with the dosage form should be included.

3. The Division has concerns about the fate of the backing material. The Sponsor states that it can be swallowed, but is it resorbable? It would seem that there is some risk of aspiration, particularly if the patient goes to sleep with the disc in place. The Sponsor should have a plan to document the fate of the backing material and should discuss the associated safety issues.

4. The Sponsor proposes to have patients treat a single ulcer, even if there are multiple ulcers present. In actual use, patients who have multiple ulcers would likely use more than one OraDisc™ at a time. The Division would prefer a trial design that permits evaluation of the safety and efficacy of the product under conditions of actual use.

5. The criteria for success were not clear from the submission. The criteria that the Division is willing to commit in advance to accept would be that in order to "win," active will have to beat vehicle and vehicle will have to be non-inferior to no treatment.

6. The Sponsor is reminded that the ICH E1a guidance recommends that in the case of a chronic use drug, a minimum of 300-600 patients be on active for at least six months. Given the safety information available about amlexanox and the fact that aphthous ulcers is an acute, short term pathology, the Agency would be willing to defer long term safety studies to Phase 4. The Sponsor should clarify its plans for assessing long term safety.

7. The Sponsor should understand that the submitted protocol as modified by FDA comments constitutes the EOP2 commitments made by the Division. Subsequent protocol amendments must be submitted to the FDA, but FDA receipt of these protocol amendments does not constitute a commitment to consider that amendment acceptable in the NDA review. Generally the Division will only contact the Sponsor regarding a protocol amendment if that amendment raises a safety concern. If the Sponsor desires FDA commitment regarding a specific protocol amendment, they should submit the amendment(s) for FDA consideration as a 45-day Special Protocol Assessment request.

Biostatistics:

1. The primary efficacy endpoint should be defined as the proportion of patients with complete healing of all ulcers. Several secondary endpoints involving pain resolution and ulcer have been proposed.

   (a) Note that although an analysis for time to healing has been proposed, it is not listed as a secondary endpoint.
   (b) The secondary endpoints will be assessed at a large number of timepoints. An adjustment for multiplicity may be necessary if the results are to be used in labeling.

2. The protocol should clarify what must be demonstrated by the pairwise comparisons among the three treatments to establish efficacy. The active treatment should be superior to vehicle, and the vehicle should be non-inferior to no treatment. A non-inferiority margin should be specified in the protocol so that non-inferiority can be assessed.

3. The protocol states that both 95% and 97.5% confidence intervals will be used "as appropriate". The protocol should clarify when it is appropriate to use the two levels. A test of hypothesis with alpha=0.05 should be used to assess the superiority of active over vehicle, and a one-sided 97.5% confidence interval (with an appropriate non-inferiority margin) should be used to assess the non-inferiority of vehicle to no treatment.

4. The method for handling missing data in the ITT population should be provided.

5. In the analysis of the primary efficacy endpoint, the Cochran-Mantel-Haenszel test should be the primary analysis, with the logistic regression being secondary. The protocol should be clear about which analysis is primary.

6. The sponsor is encouraged to use a limited number of covariates in the logistic regression and log-rank models. For a confirmatory trial, only a small number of covariates should be specified in the protocol, and all of the specified covariates should be retained in the final model. This method is preferred over testing all possible covariates for significance in confirmatory trials.

7. The protocol should include a method of assessing treatment by center interaction in the primary analysis.

8. The Division recommends enrolling at least 10 subjects per treatment arm per center to avoid problems with small centers in the analysis. However, the protocol should also specify a plan for combining centers (based on the number of patients, or geographic region) in case the enrollment targets are not met.

All comments are based upon the briefing document, which is an unofficial document submitted as information. The final protocols should be submitted to the IND for review.

Pediatric Studies:
The Food and Drug Administration Modernization Act [FDAMA] of 1997, Section 111, Pediatric Studies of Drugs, effective April 1, 1999, requires the following: Per 21 CFR 314.50(d)(7), NDA applications are required to *contain a section describing the investigation of the drug for use in pediatric populations, including an integrated summary of the information (the clinical pharmacology studies, controlled clinical studies, or uncontrolled clinical studies, or other data or information) that is relevant to the safety and effectiveness and benefits and risks of the drug in pediatric populations for the claimed indications, and information required to be submitted under Section 314.55.*

In addition, per 21 CFR 314.55(a), each NDA *application for a new ingredient, new indication, new dosage form, new dosing regimen, or new route of administration shall contain data that are adequate to assess the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations, and to support dosing and administration for each pediatric subpopulation for which the drug is safe and effective.* Under 21 CFR 314.55(d) *this section does not apply to any drug for an indication or indications for which orphan designation has been granted under part 316, subpart C, of this chapter.* A waiver can be requested in accordance with 21 CFR 314.55(c).

Financial Disclosure:
The Final Rule regarding Financial Disclosure was published on February 2, 1998, for applications submitted after February 2, 1999, the applicant is required either to certify the absence of certain financial interests and arrangements of clinical investigators or to disclose those financial interests.

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