CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-965

MEDICAL REVIEW(S)

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Medical Officer's Review of NDA 20-965, AZ Submission

Correspondence date: 10/01/99
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SPONSOR: DUSA Pharmaceuticals

DRUG: LEVULAN KERASTICK (aminolevulinic acid HCl) for Topical Solution, 20% (LEVULAN)

PHARMACOLOGIC CATEGORY: Anti-neoplastic photosensitizer

PROPOSED INDICATION: Treatment of actinic keratoses (AKs) of the face or scalp

DOSAGE FORM/ROUTE OF ADMINISTRATION: Solution, applied topically to actinic keratosis lesions

BACKGROUND:
On June 27, 1999, Agency notified Sponsor that NDA 20-965 was approvable. Agency informed Sponsor that before approval, satisfactory inspections will be required for all manufacturing and testing facilities, and revised draft labeling must be submitted. Revised draft labelling was submitted as part of this submission and has been reviewed and revised by Agency. Labeling that incorporates Agency revisions of sponsor's draft revised label is appended to the review of this submission.

Four informational needs of clinical relevance were identified:

- Characterization of the potential for dermal irritancy with LEVULAN.
- Characterization of the potential for dermal allergenicity with LEVULAN.
- Characterization of the safety and efficacy of LEVULAN in an additional 70 patients. At least 30 of the additional patients should have Fitzpatrick skin types IV-VI. Follow-up at one year after treatment should be arranged to assess the long term recurrence rate of actinic keratoses that have resolved after treatment.
- Characterization of the safety and efficacy of LEVULAN for the treatment of AKs of the [redacted]

Sponsor was also requested to update the NDA by submitting all safety information pertinent for LEVULAN accumulated since the date of the original NDA submission.

On November 5, 1999, at a meeting of the Dermatologic and Ophthalmic Drug Advisory Committee, several committee members expressed concern that because LEVULAN action may cause oxidative DNA damage, and because treatment with LEVULAN does not always result in permanent, complete clearing of AK lesions, the possibility exists that LEVULAN treatment may enhance the oncogenic progression of AK lesions that are

not permanently, completely resolved by LEVULAN treatment. Several committee members also expressed interest in having a patient package insert prepared for the drug product. Agency's revision of sponsor's draft patient package insert is appended to this submission review.

AZ SUBMISSION SUMMARY:
Sponsor has committed to characterize the potential for dermal sensitization with LEVULAN and characterize the safety and efficacy of LEVULAN in an additional 70 patients, including patients with Fitzpatrick skin types IV-VI, and to assess the long tem recurrence rate of AK lesions over a 12-month follow-up period. Sponsor has provided a justification for not undertaking a characterization of the safety and efficacy of LEVULAN for the treatment of AKs of the back and arms, and for not undertaking a characterization of the potential for dermal irritancy with LEVULAN. Sponsor has submitted in tabular form safety data from the results of trials that were still ongoing at the time of NDA submission.

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Following the Draft Guidance *Skin Irritation and Sensitization Study (Modified Draize Test),* Sponsor plans a controlled study on LEVULAN

Reviewer's Comment:
The outline of the protocol for the study is satisfactory, and as outlined would address the informational need to characterize the Sponsor is encouraged to submit the final study protocol prior to study initiation.

Sponsor suggests that characterization of the cumulative irritancy of LEVULAN should not be required. The most compelling consideration that such a study is not necessary is that LEVULAN is unique among dermatological drugs in that it would only be applied once or twice to any given skin site. The relevancy of a cumulative irritancy study for such a product is unclear.

- Characterization of the safety and efficacy of LEVULAN for the treatment of AKs of the

Sponsor notes that the drug dose-ranging and light dose-ranging studies that were undertaken to establish the treatment parameters related to LEVULAN use were designed for treatment of AKs of the face or scalp, and may not be optimal for treatment of lesions at other body sites. In particular,

The sponsor states that

Reviewer's Comment:
Because the sponsor makes several compelling arguments that characterization of the safety and efficacy of LEVULAN for treatment of AKs of the is not warranted at this time, withdrawal of the request by Agency for

is appropriate at this time.

- Characterization of the risk of malignant progression of AK lesions that do not undergo complete, permanent clearing after treatment with LEVULAN.

Numerous epidemiologic studies, as well as the clinical experience of dermatologists, have established that AKs are pre-cancerous skin lesions, with a low risk of malignant progression to squamous cell carcinoma of the skin. The theoretical possibility cannot be excluded that LEVULAN-induced oxidative DNA damage may promote the malignant progression of AKs that are incompletely cleared or that recur after LEVULAN treatment. As part of the approval letter, sponsor should be asked to address this possibility by committing to perform a clinical study involving long-term (at least 12 month follow-up) of treated patients. A goal of this study should include characterization of the recurrence rate at 12 months of AK lesions that cleared by the primary endpoint (e.g., 8 weeks). In addition, this study should also characterize the histopathology of AK lesions in long-term follow-up. The following discussion concerning the histopathology of different grades of AK lesions is based on the article "Incipient Intraepidermal Cutaneous Squamous Cell Carcinoma: A Proposal for Reclassifying and Grading Solar (Actinic) Keratoses", by Yantos et al., Semin. Cutan. Med. and Surg., Vol. 18, No. 1, 3/99, pp. 3-14.

All AK lesions are characterized by atypical keratinocytic proliferation in the epidermis. AK lesions that are hypothesized to have undergone comparatively less malignant progression are characterized by atypical keratinocytic proliferation confined to the lower one-third or lower two-thirds of the epidermis. AK lesions that are hypothesized to have undergone comparatively more malignant progression are characterized by atypical keratinocyte proliferation involving the full thickness of the epidermis including adnexal structures. Lesions in which there is extension of neoplastic cells from the epidermis into the papillary or reticular dermis are considered squamous cell carcinoma of the skin. The hypothesis that sponsor's study should be designed to reject is that AK lesions that are (a) completely cleared; (b) completely cleared but recur during follow-up; and (c) not completely cleared carry an increased risk of either (1) atypical keratinocyte proliferation involving the full thickness of the epidermis including adnexal structures, or (2) squamous cell carcinoma of the skin. Sponsor should estimate the spontaneous incidence of progression of actinic keratoses to squamous cell carcinoma of the skin based on a review of the relevant scientific literature, and based on this estimate, should characterize the histopathology of enough treated lesions to preclude the possibility that a clinically significant fraction of completely cleared, completely cleared but recurrent, or not completely cleared lesions undergo malignant progression to full thickness epidermal atypia or to squamous cell carcinoma of the skin as a consequence of treatment.

- Sponsor's update of NDA, with submission of all safety information pertinent for LEVULAN accumulated since the date of the original NDA submission.

Sponsor submitted the safety results from [redacted] ongoing

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