CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20-986/SE3-003

MEDICAL REVIEW(S)

MEDICAL OFFICER REVIEW

DIVISION OF METABOLIC AND ENDOCRINE DRUG PRODUCTS (HFD-510)

APPLICATION #:	**#20986**	**APPLICATION TYPE:**	**NDA: Supplement**
SPONSOR:	**NovoNordisk**	**PROPRIETARY NAME:**	**NovoLog**
CATEGORY OF DRUG:	**Diabetes** **Insulin analogue**	**USAN / Established Name:** **ROUTE:**	**X-14, Insulin aspart** **SQ infusion via external pump**
MEDICAL REVIEWER:	**Elizabeth Koller**	**REVIEW DATE:**	**12/20/01**

SUBMISSIONS REVIEWED IN THIS DOCUMENT

Document Date:	CDER Stamp Date:	Submission Type:	Comments:
12/20/00	12/21/00	SE3-003	
2/7/01	2/8/01	SE3-003 C	
2/28/01	2/28/01	SE3-003 IN	
3/6/01	3/6/01	SE3-003 IN	
3/7/01	3/7/01	SE3-003 IN	
3/22/01	3/23/01	N-000 C	Comments on spreadsheet request
6/21/01	6/22/01	SE3-003 BM	EXCEL spread sheets
8/29/01	8/29/01	SE3-003 IN	
10/5/01	10/5/01	P-004	Adverse event reports suggesting injection/infusion site reactions, insulin instability, and infusion set occlusion
10/24/01	10/25/01	SE3-003 BL	
10/25/01	10/26/01	SE3-003 BC	
12/11/01	12/13/01	SE3-003 BL	
12/12/01	12/13/01	SE3-003 BL	
12/17/01	12/17/01	SE3-003 IN	
12/18/01	12/20/01	SE3-003 C	
12/19/01	12/20/01	SE3-003 BL	
12/21/01	12/21/01	SE3-003 IN	

RELATED APPLICATIONS (if applicable)

Document Date:	APPLICATION Type:	Comments:
12/21/99	NDA #20563 SE3-024	Pump supplement
Multiple	NDA #20563 Periodic reports	Adverse events
Multiple	IND [redacted]	[redacted]

Overview of Application/Review:

Three, randomized, open-label, parallel-design studies of varying lengths were conducted in the U.S. in adult patients with variable degrees of diabetic control. Pump studies comparing glycemic control (HgbA1c) using different types of insulin were conducted in IDDM patients already familiar pump therapy. Studies in NIDDM patients new to intensive insulin therapy were conducted to compare glycemic control (HgbA1c) using X-14 injection versus X-14 infusion therapy. The design of the clinical studies differed substantively from standard

medical practice and typical use in real life, with more frequent changes of insulin, infusion sets, and infusion sites, Glycemic control and rates of hypoglycemia were comparable for the various treatment arms in all three studies. The data from the smallest study (018; n=29) suggested that the time to infusion set failure/occlusion was shorter and the number of infusion set changes greater in the X-14 treatment arm than in the buffered human insulin arm. Although data on infusion set changes were also collected in the two, larger studies, these data were not provided. In addition, even though *in vitro* data indicated that X-14 consistently failed in the Mini-Med 506 pump on day 3, no correlation with the clinical data could be made because there were no records of the specific pumps used by individual patients.

Outstanding Issues:.

1-X-14 can be approved for use in specific pumps with specific infusion sets. Approval cannot be extrapolated to other equipment. The X-14 insulin, infusion sets, and infusion sites may be used for up to 48 hours.

2-Because the design of the clinical studies differed substantively from standard medical practice and typical use in real life, with more frequent changes of the insulin, infusion sets, and infusion sites, the consequences of such deviations from recommendations should be delineated in both the physician and patient labels. Because current standard practice reflects the large reservoir size, the software restrictions for reducing the amount of insulin inserted into the reservoir, and pump manufacturers' printed instructions (including changing tubing every three days), the physician and patient labels must clearly indicate that the directions for the specific use of X-14 in pumps supercede the manufacturers' general guidelines.

3-The sponsor should collect information on actual-use either in a phase four study in which insulin and infusion sets are not provided or via collection of adverse event data systematically using a questionnaire specifically designed to identify the causes of pump-insulin problems.

4-New pump guidelines should be developed.

Recommended Regulatory Action:

New Clinical Studies: _____ **Clinical Hold** _____ **Study May Proceed**

NDAs:

Efficacy / Label Supp.: with label changes & appropriate follow-up of pump/insulin malfunction **Approvable**

_____ _____ **Not Approvable** _____

Signed: **Medical Reviewer:** /S/ Elizabeth Koller, M.D. **Date:** 12/2101

Medical Team Leader: _____ **Date:** _____

APPEARS THIS WAY
ON ORIGINAL

1.-Medical Officer Review

1.1.-Administrative summary

1.1.1.-NDA: #20986 SE3

1.1.2.-Review: #1

1.1.3.-Submissions:

1.1.3.1.-Paper submission:12/21/00

1.1.3.2.-CANDA submission: none

1.1.3.3.-Major amendment: none

1.1.3.4.-Other submissions:

2/7/01 SE3-003 C
2/28/01 SE3-003 IN
3/6/01 SE3-003 IN
3/7/01 SE3-003 IN
3/22/01 N-000 C comments on spread sheet request
6/21/01 SE3-003 BM Excel spread sheets
8/29/01 SE3-003 IN
10/5/01 P-004 adverse event reports suggesting skin reactions, insulin instability, & infusion set occlusion
10/24/01 SE3-003 BL
10/25/01 SE3-003 BC
12/11/01 SE3-003 BL
12/12/01 SE3-003 BL
12/17/01 SE3-003 IN
12/18/01 SE3-003 C
12/19/01 SE3-003 BL
12/18/01 SE3-003 IN

1.1.3.5.-Review completed: 12/21/01

1.2.-Drug name

1.2.1.-Generic name: insulin aspart

1.2.2.-Trade name: NovoLog

1.3.-Sponsor: NovoNordisk

1.4.-Pharmacologic category: diabetes, insulin analogue

1.5.-Proposed indication: use in external pumps for subcutaneous infusion

1.6.-Dosage form and route-of administration:

1.6.1.-Dosage form: vials for extraction of insulin that is to be put into a pump reservoir

1.6.2.-Dosage: to be titrated using pre-prandial boluses and basal rates of continuous infusion

1.6.3.-Route-of-administration: subcutaneous infusion

1.7.-NDA drug classification: standard

1.8.-Important related drugs: human insulin (semi-synthetic and recombinant)
Lilly buffered human insulin, BR
(approved; no longer marketed)
NovoNordisk buffered human insulin, Velosulin
lispro

1.9.- Related reviews: NDA #20563 pump reviews and adverse event reports

1.10.-Materials reviewed:

1.10.1.-NDA #20986

12/20/000 SE3-003 (38 volumes)
2/7/01 SE3-003 C
2/28/01 SE3-003 IN
3/6/01 SE3-003 IN
3/7/01 SE3-003 IN
3/22/01 N-000 C comments on spread sheet request
6/21/01 SE3-003 BM Excel spread sheets
8/29/01 SE3-003 IN
10/5/01 P-004 adverse event reports suggesting skin reactions, insulin instability, & infusion set occlusion
10/24/01 SE3-003 BL
10/25/01 SE3-003 BC
12/11/01 SE3-003 BL
12/12/01 SE3-003 BL
12/17/01 SE3-003 IN
12/18/01 SE3-003 C
12/19/01 SE3-003 BL
12/18/01 SE3-003 IN

1.10.2.-Other

Draft pump guidance (1985) (appendix 1)
Velosulin label
Pump questionnaire developed by Dr. Koller in response to questions raised by A. Morrison (Devices) and adverse event reports; 10/10/99
Internal e-mail regarding composition of tubing and needles for various infusion sets (P. Cricenti and V. Nakayama; 11/28/00)
Mini-Med pump video and print information
Disetronic pump video and print information
Pump chat room

1.10.3.-Safety update: none submitted

1.11.-Table of contents

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.