

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 021028

MICROBIOLOGY REVIEW(S)

Free

JAN 29 1999

REVIEW FOR HFD-510
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW #2 OF NDA 21-028
27 January 1999

- A. 1. NDA 21-028 BI
APPLICANT: Novo Nordisk Pharmaceuticals, Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
2. PRODUCT NAME: Velosulin BR® Human Buffered Regular Human
Insulin Injection (recombinant DNA origin)
3. DOSAGE FORM AND ROUTE OF ADMINISTRATION:
The product is a sterile injectable preparation for continuous subcutaneous
insulin infusion.
4. METHODS OF STERILIZATION:
[REDACTED]
5. PHARMACOLOGICAL CATEGORY and/or PRINCIPLE INDICATION:
The drug product is indicated in the treatment of diabetes mellitus.
- B. 1. DATE OF INITIAL SUBMISSION: 22 July 1998
2. DATE OF AMENDMENT: 23 December 1998 (Subject of this
Review)
3. RELATED DOCUMENTS: IND [REDACTED]
4. ASSIGNED FOR REVIEW: 4 January 1999
- C. REMARKS: The product will be manufactured by:

Novo Nordisk A/S
Novo Alle
DK-2880 Bagsvaerd
Denmark

Novo Nordisk, NDA 21-028, Velosulin BR[®], Microbiologist's Review #2

D. CONCLUSIONS: The application is recommended for approval on the basis of sterility assurance.

/S/

[REDACTED]

27 January 1999

Paul Stinavage, Ph.D.

/S/

[REDACTED]

1/29/99

cc: Original NDA 21-028
HFD-510/J. Rhee/Div. File
HFD-805/Consult File/Stinavage

Drafted by: P. Stinavage, 27 January 1999
R/D initialed by P. Cooney

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NOV 18 1998

REVIEW FOR HFD-510
OFFICE OF NEW DRUG CHEMISTRY
MICROBIOLOGY STAFF
MICROBIOLOGIST'S REVIEW OF NDA 21-028
16 November 1998

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The drug product is indicated in the treatment of diabetes mellitus.

B. 1. DATE OF INITIAL SUBMISSION: 22 July 1998

2. DATE OF AMENDMENT: (none)

3. RELATED DOCUMENTS: IND

4. ASSIGNED FOR REVIEW: 17 August 1998

C. REMARKS: The product will be manufactured by:

Novo Nordisk A/S
Novo Alle
DK-2880 Bagsvaerd
Denmark

Novo Nordisk, NDA 21-028, Velosulin BR®, Microbiologist's Review #1

D. CONCLUSIONS: The application is approvable pending resolution of microbiology concerns.

/S/ [Redacted]

16 November 1998

Paul Stinavage, Ph.D.

/S/ [Redacted]

11/19/98

cc: Original NDA 21-028
HFD-510/J. Rhee/Div. File
HFD-805/Consult File/Stinavage

Drafted by: P. Stinavage, 16 November 1998
R/D initialed by P. Cooney

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 021028

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**



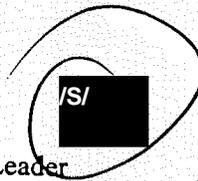
DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: 4/19/99

From: Saul Malozowski
Acting Medical Team Leader



Subject: Velosulin, NDA 21-028

To: Solomon Sobel
Division Director, DMEDP

The reviews of the documentation provided by the sponsor indicate that Velosulin of recombinant origin is bioequivalent to its semisynthetic form. Therefore, in supporting the reviewer's conclusions I am recommending approval of this submission.

cc: Orig NDA 21-028
HFD-510/Div File

Team Leader's Comments

I concur with the HO's review
I also need approval of [redacted] [redacted]
ACR 116 [redacted] 12/8/98

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JAN 22 1999

Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-028
Buffered Regular Human Insulin (rDNA origin) (Velosulin BR®)	
Submission Date:	22 July 1998 28 September 1998
Sponsor:	Novo Nordisk
Type of Submission:	Original NDA
Reviewer:	Michael J. Fossler

Submission

The submission dated 7/22/98 and amended 9/28/98 is for Velosulin, a buffered human insulin for use in insulin pumps. The current formulation used insulin derived from a semi-synthetic process, in which porcine insulin undergoes an enzymatic conversion to human insulin. The product proposed for marketing under the current submission is identical to the currently-marketed product, except the insulin is manufactured using recombinant DNA technology.

An open-label, single-dose randomized crossover study in normal volunteers was conducted to determine if the new formulation is bioequivalent to the marketed semi-synthetic product.

Study Design

TITLE OF TRIAL

An open label, two period, crossover study in healthy male volunteers to test the bioequivalence between Velosulin Regular Buffered human insulin recombinant DNA and Velosulin Buffered human insulin semi-synthetic origin

OBJECTIVES

The objective of this investigation was to evaluate the bioequivalence of Velosulin Regular Buffered human insulin recombinant DNA origin, 100 u/mL and Velosulin Regular Buffered human insulin semi synthetic origin, 100 u/mL.

METHODOLOGY

This was a single site, open label, two period, crossover study with a one week washout between single doses of study drug. The order of treatments were randomized. At screening and on study completion, study day 2, subjects had a physical examination, a Complete Blood Count and Blood Chemistry performed to ensure they are healthy at entry and exit of the study. Fasting subjects received a different insulin injection on study days 1 and 2, as predetermined by the randomization schedule. Twelve hour insulin, glucose and C-Peptide profiles were obtained for each subject. The design was standard for a single dose bioequivalence study. The one week washout period allowed complete elimination of study drug and met the FDA requirement for the washout period to exceed 5 elimination half lives.

NUMBER OF SUBJECTS

Twenty-six healthy adult male volunteers between 18 and 40 years of age.

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DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION

- Men between 18 and 40 years inclusive.
- BMI > 20 and < 27 kg/m²
- Considered to be healthy upon completion of medical history, and physical examination.
- Provision of written informed consent prior to fasting or any study procedure.
- FBG < 105 mg/dL

TEST PRODUCT, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

Velosulin R Buffered Human Insulin Recombinant DNA Origin 100 u/mL 10 mL Vials, 0.1 u/kg body weight, subcutaneous injection, Batch No. 6D94115

DURATION OF TREATMENT

10 days

REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION, BATCH NUMBER

Velosulin R Buffered Human Insulin Semi Synthetic Origin 100 u/mL 10 mL Vials, 0.1 u/kg body weight, subcutaneous injection, Batch No. 6K84107

CRITERIA FOR EVALUATION - EFFICACY

The primary endpoint for bioequivalence following subcutaneous insulin administration was:

- 1) a comparison of AUC and C_{max} for immunoreactive insulin (IRI) for the two insulin products.

The secondary endpoints for bioequivalence following subcutaneous insulin administration were:

- 2) an assessment of T_{max} , T_{min} , C_{min} for IRI.
- 3) an assessment of C-Peptide and glucose profiles.

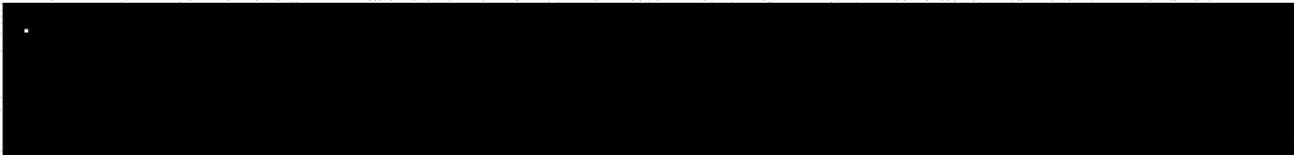
STATISTICAL METHODS

Analysis of the primary endpoints was a standard cross-over analysis on the logarithm of the AUCs and C_{max} between 0-720 minutes. The mean difference (log AUC and log C_{max}) between preparations was estimated and a 90% confidence interval for the mean difference calculated.

The estimated mean difference and confidence interval were then re-transformed to give an estimate of the ratios (rDNA/semi synthetic for AUC and C_{max} , probably C_{min}) and a 90% confidence interval for the ratio. The latter should have been completely contained in the 80%-125% interval in order to declare bioequivalence.

Insulin, Glucose, and C-Peptide results have been displayed graphically.

All data including demographic and safety data were listed. Laboratory data were flagged if outside the reference range. Laboratory data were analyzed for significant changes from pre- to post study. A significance level of 5% was used for these analyses.



The assay cross-reacts to a significant extent with proinsulin; however, this is of little clinical significance, since proinsulin levels are extremely low in healthy individuals. Overall, the assay is satisfactorily validated.

Results

Insulin

Mean pharmacokinetic parameters and results of the two one-sided test procedure results for insulin are shown in Table 2. Figure 1 shows a plot of the mean concentration profile as a function of time. Based on these data, the two formulations appear to be bioequivalent.

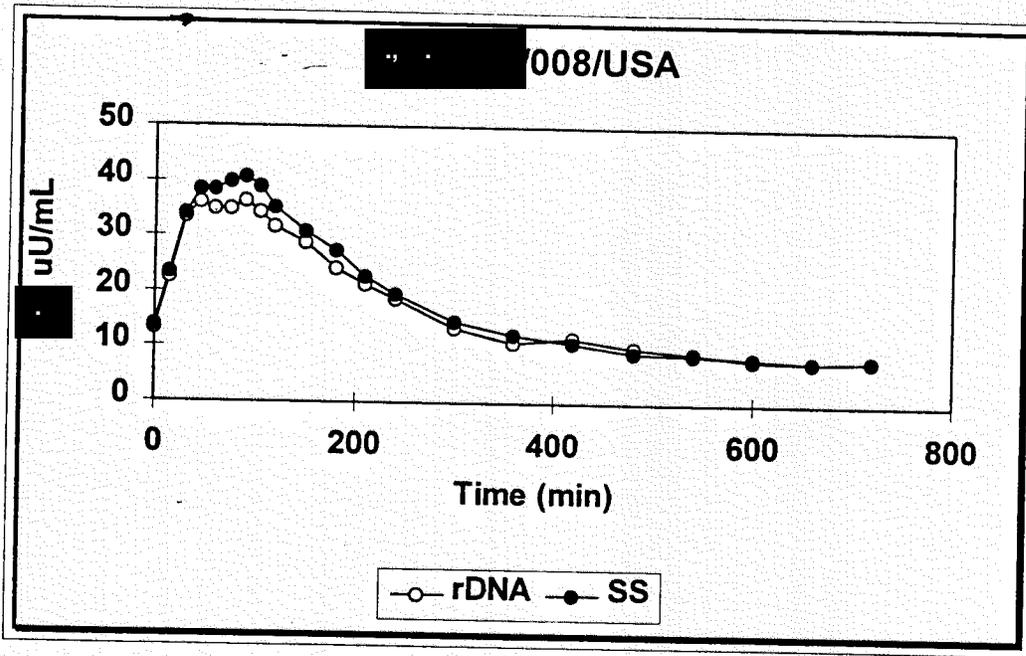
Table 2: Mean pharmacokinetics for insulin after the two treatments and results of two one-sided test procedure.

Parameter	rDNA	[†] Semi-Synthetic	90% CI
AUC(0-last) (mU • min/mL)	12.06 ± 2.25	12.53 ± 3.12	0.974 (0.94, 1.01)
Cmax (μU/ml)	44.0 ± 14.0	46.3 ± 12.1	0.941 (0.87, 1.02)
^{**} tmax (min)	90 (30.0 - 150.0)	75 (30.0 - 360)	na

[†]reference

^{**}median (range)

Figure 1: Mean plasma insulin concentrations for the two formulations.



C-peptide, glucose

The results for the assessment of c-peptide and glucose are shown in Table 3. The results appear to support the insulin findings. For c-peptide, the 90% confidence interval for Cmin is not contained within 80-125, although the point estimate is 0.898. This may be due to variability.

Table 3: Mean parameters and results of two one-sided t- test procedure for c-peptide and glucose

Parameter	rDNA	[†] Semi-Synthetic	90% CI
C-peptide			
AUC(0-last) ($\mu\text{g} \cdot \text{min}/\text{mL}$)	536.4 \pm 130.6	556.1 \pm 165.3	0.977 (0.91, 1.05)
Cmin (ng/ml)	0.38 \pm 0.18	0.41 \pm 0.18	0.898 (0.73, 1.10)
tmin (min)	210 (105 - 360)	210 (105 - 420)	na
Glucose			
AUC(0-last) (g \cdot min/dL)	54.8 \pm 3.7	55.3 \pm 4.9	0.992 (0.97 - 1.01)
Cmin (mg/dL)	56.04 \pm 9.3	56.6 \pm 9.7	0.992 (0.94, 1.05)
^{††} tmin (min)	112.5 (60.0 - 360)	105 (45.0 - 360)	na

[†]reference
^{††}median (range)

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Conclusions

- 1) Based on the analysis of plasma insulin concentrations after a 0.1 U/kg dose of each of the two insulin preparations, the recombinant insulin is bioequivalent to the currently-marketed semi-synthetic product.

Recommendations

The Office of Clinical Pharmacology and Biopharmaceutics recommends approval of NDA 21-028. There are no comments to the firm at this time.

/s/ [Redacted]

Michael J. Fossler, Pharm.D., Ph.D.

Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics /s/ [Redacted]

FT initialed by Hae-Young Ahn, Ph.D., Team Leader [Redacted]

CC: NDA 21-028(orig., 1 copy), HFD-510(Rhee, J., Misbin), HFD-850(Lesko), HFD-870(M.Chen, Fossler, Ahn), Central Document Room(Barbara Murphy)
2/24/98

Optional Intra-Divisional Briefing held 1/22/99: Present: Chen, Ahn, Fossler

Recommendation Code: AP

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SUMMARY OF HUMAN PHARMACOKINETICS

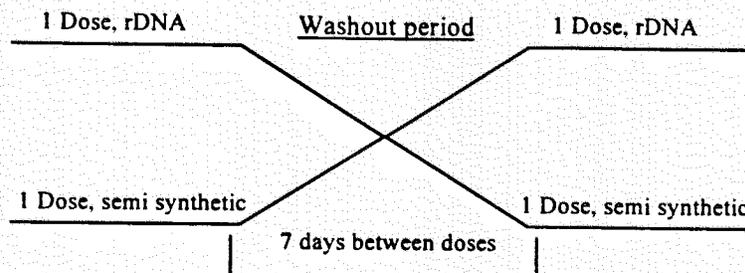
Study [REDACTED]/008/USA was conducted to evaluate the bioequivalence of Velosulin Regular Buffered human insulin recombinant DNA origin, 100 u/mL and Velosulin Regular Buffered human insulin semi synthetic origin, 100 u/mL.

TEST PRODUCTS USED IN STUDY [REDACTED]/008/USA

TEST PRODUCT	DOSE (Duration)	MODE OF ADMINISTRATION	BATCH NUMBER
Velosulin R Buffered Human Insulin Recombinant DNA Origin 100 u/mL 10 mL Vials	0.1 u/kg body weight (Single Dose)	subcutaneous injection	6D94115
Velosulin R Buffered Human Insulin Semi Synthetic Origin 100 u/mL 10 mL Vials	0.1 u/kg body weight (Single Dose)	subcutaneous injection	6K84107

Study Design

This was a single site, open label, two period, crossover study with a one week washout between single doses of study drug. The order of treatments were randomized. Twenty-six healthy adult male volunteers between 18 and 40 years of age were enrolled. Fasting subjects received a different insulin injection on study days 1 and 2. The figure below illustrates the study design of [REDACTED]/008/USA:



On dosing Day 1 and Day 2, the blood samples were taken for serum analysis at -15, 0, 15, 30, 45, 60, 75, 90, 105, 120, 150, 180, 210, 240, 300, 360, 420, 480, 540, 600, 660, and 720 minutes relative to each Velosulin injection. AUC, C_{max}, T_{max}, C_{min} and T_{min} were calculated for insulin, C-Peptide, and glucose.

Statistical Methods

Analysis of the primary endpoints was a standard cross-over analysis on the logarithm of the AUCs and C_{max} between 0-720 minutes. The mean difference (log AUC and log C_{max}) between preparations was estimated and a 90% confidence interval for the mean difference calculated.

The estimated mean difference and confidence interval were then re-transformed to give an estimate of the ratios (rDNA/semi synthetic for AUC and C_{max}) and a 90% confidence interval for the ratio. The latter should have been completely contained in the 80%-125% interval in order to declare bioequivalence.

Demographics

Twenty-six male subjects ranging in age from 19 to 40 years and predominately divided almost equally between white (n=11) and black (n = 12) were enrolled in this study. The distribution of subjects by baseline demographic characteristics in the 2 treatment sequences was comparable.

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Pharmacokinetic and Pharmacodynamic Results

Insulin

Velosulin recombinant DNA origin and semi synthetic origin were found to be bioequivalent based on AUC and C_{max} . There were no significant differences measured between therapies, as shown below:

RESULTS FOR INSULIN PHARMACOKINETIC PARAMETERS

Parameter	rDNA n = 24	semi synthetic n = 24	Ratio (90% CI)	p-value
Primary Variables				
AUC_{insulin} (min·uU/mL)				
Mean (SD)	12058.88 (2253.59)	12529.72 (3120.16)	0.974	0.268
Median	11286.38	11568.75	(0.94, 1.01)	
Range	8130.75 - 16881.00	8108.25 - 19509.00		
C_{max} (insulin) (uU/mL)				
Mean (SD)	44.00 (13.99)	46.27 (12.11)	0.941	0.191
Median	42.35	47.45	(0.87, 1.02)	
Range	26.10 - 90.70	28.40 - 83.60		
Secondary Variables				
C_{min} (insulin) (uU/mL)				
Mean (SD)	6.95 (2.46)	6.77 (2.39)	1.019	0.624
Median	6.50	6.05	(0.95, 1.09)	
Range	3.00 - 12.40	3.50 - 13.80		
T_{max} (insulin) (min)				
Mean (SD)	90.63 (36.34)	90.63 (63.25)	0.000*	0.519
Median	90.00	75.00		
Range	30.00 - 150.00	30.00 - 360.00		
T_{min} (insulin) (min)				
Mean (SD)	625.00 (90.07)	582.50 (103.89)	60.00*	0.173
Median	660.00	600.00		
Range	360.00 - 720.00	360.00 - 720.00		

a - Difference for T_{max} and T_{min} . P-values and 90% CI for between group comparison in AUC, C_{max} , C_{min} , were calculated from ANOVA based on the crossover model, using log-transformed data. For secondary variables, T_{max} and T_{min} , the differences between test and reference groups were estimated as the median of the difference within each subject, using raw data, the p-values were calculated using Signed Rank test.

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C-Peptide

Velosulin recombinant DNA origin and semi synthetic origin were found to be similar when comparing secondary pharmacodynamic parameters measured for C-Peptide response in subjects after a single dose of each drug. There were no significant differences measured between therapies, as shown below:

PHARMACODYNAMIC PARAMETERS FOR C-PEPTIDE PROFILE

	rDNA n = 24	semi synthetic n = 24	Ratio / Difference (90% CI)	p-value
AUC₀₋₇₂₀ (min · ng/mL)				
Mean (SD)	536.39 (130.60)	556.08 (165.30)	0.977	0.566
Median	532.43	511.09	(0.91, 1.05)	
Range	351.75 - 792.00	343.35 - 943.13		
C_{min} (ng/mL)				
Mean (SD)	0.38 (0.18)	0.41 (0.18)	0.898	0.382
Median	0.34	0.37	(0.73, 1.10)	
Range	0.13 - 0.80	0.13 - 0.90		
T_{min} (min)				
Mean (SD)	226.88 (66.69)	220.63 (77.94)	0.000	0.566
Median	210.00	210.00	(NA)	
Range	105.00 - 360.00	105.00 - 420.00		

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Glucose

Velosulin recombinant DNA origin and semi synthetic origin were found to be similar when comparing secondary pharmacodynamic parameters measured for glucose response in subjects after a single dose of each drug. There were no significant differences measured between therapies, as shown below:

PHARMACODYNAMIC PARAMETERS FOR GLUCOSE PROFILE

Parameter	rDNA n = 24	semi synthetic n = 24	Ratio / Difference (90% CI)	p-value
AUC₀₋₇₂₀ (min · mg/dL)				
Mean (SD)	54788.13 (3688.18)	55324.69 (4894.73)	0.992	0.471
Median	54626.25	54851.25	(0.97, 1.01)	
Range	46680.00 - 63420.00	45945.00 - 67755.00		
C_{min} (mg/dL)				
Mean (SD)	56.04 (9.30)	56.58 (9.68)	0.992	0.805
Median	57.00	59.00	(0.94, 1.04)	
Range	38.00 - 73.00	33.00 - 76.00		
T_{min} (min)				
Mean (SD)	151.25 (91.39)	135.00 (81.56)	0.000	0.358
Median	112.50	105.00	(NA)	
Range	60.00 - 360.00	45.00 - 360.00		

Conclusion

Velosulin R Buffered Human Insulin Semi Synthetic Origin 100 u/mL and Velosulin R Buffered Human Insulin Recombinant DNA Origin 100 u/mL were found to be bioequivalent.

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Draft Labeling**