

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 021028

ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

**RECORD OF TELEPHONE
CONVERSATION/MEETING**

Date:
July 1, 1999

Re: 6/30/99 fax (attached)

I called Mr. Barbush and informed him that we agree with the most of their proposed changes as outlined in their 6/30/99 fax. However, I informed him that we do not agree with the following two proposed changes and asked him not to make these changes. These two changes are:

1. Deletion of **DRAFT LABELING** under WARNINGS section, and
2. Deletion of **DRAFT LABELING** and an addition of **DRAFT LAB** under TYPES OF INSULINS.

I informed Mr. Barbush that I will be away between 7/8 and 7/14 and asked him when I could expect their response. He replied that he will try to get back to me this afternoon.

cc:OrigNDA
HFD-510/DivFile
HFD-510/Misbin/Berlin/Steigerwalt

21-028#:

**Telecon/Meeting
initiated by:**

FDA

By: Telephone

Product Name:
Velosulin BR (rDNA)

Firm Name:
Novo Nordisk

**Name and Title of Person
with whom conversation
was held:**

Mr. Michael Barbush
Regulatory Affairs

Phone:
(609) 987-5973

/SI

7-1-99

Name: Julie Rhee

MEMORANDUM

DATE: June 25, 1999

FROM: Solomon Sobel, M.D. [REDACTED] 6/28/99
Director
Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: NDA 21-028 Velosulin BR (rDNA origin) Package Insert

TO: NDA 21-028 file

The pending NDA 21-028 Velosulin BR (rDNA origin) injection is a similar product as currently available Velosulin BR (semi-synthetic) injection (NDA 19-450), which was approved on May 30, 1986. The difference between these two insulin products is the method of manufacture. The NDA 19-450 is a semi-synthetic buffered regular insulin and the NDA 21-028 is a rDNA buffered regular insulin.

The package insert of currently available Velosulin BR (semi-synthetic) states that Velosulin BR (semi-synthetic) has been tested only in [REDACTED] pumps, using the accompanying [REDACTED] as well as both [REDACTED] infusion sets. The package insert also states that [REDACTED] pumps are equivalent.

According to the CDRH, when insulin external pumps get their 510(k) clearance, the pump is not cleared with specific insulin(s) to be used with the pump.

However, since the drug product in this NDA, which is a drug/device combination, was tested with MiniMed® pump alone, we cannot request the sponsor of the NDA to include other external pumps on the package insert without any supporting data.

Attachment: Copy of the 6/8/99 e-mail from Ms. Kim Dettelbach, General Counsel.

cc: Orig NDA
HFD-510/DIV File

[REDACTED] APPEARS THIS WAY ON ORIGINAL

Patent Certification

In the opinion and to the best knowledge of Novo Nordisk, there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs. This declaration is made in accordance with 21 CFR 314.53 (c) (3).



Barry Reit, Ph. D.
Vice President
Regulatory Affairs

22-July 1998
Date

EXCLUSIVITY SUMMARY FOR NDA # 21-028

SUPPL # n/a

Trade Name Velosulin BR Human, Buffered Regular Human Insulin Injection (rDNA origin) Generic Name Human Buffered Regular Human Insulin Injection (rDNA origin)

Applicant Name Novo Nordisk Pharm. HFD # 510

Approval Date If Known _____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain 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 an original NDA?
YES / X / NO / ___ /

b) Is it an effectiveness supplement?
YES / ___ / NO / X /

If yes, what type? (SE1, SE2, etc.) _____

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 /___/ NO /x/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

No

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /x/ NO /___/

If yes, NDA # 19-450 . Drug Name Velosulin BR (semi-synthetic)
NDA 19-938 Novolin R

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /___/

IF THE ANSWER TO QUESTION 3 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 /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____

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.)

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. 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 /___/ 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 /___/ 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 /___/ 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 / ___ /

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 / ___ /

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:

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.

(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 / ___ /

If yes, explain: _____

/s/



4-14-99

Signature

Date

Title: *Project Manager*

/s/



7/8/99

Signature of Office/

Date

Division Director

cc: Original NDA

Division File

HFD-93 Mary Ann Holovac

APPEARS THIS WAY ON ORIGINAL

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # 21-028 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5
SE6

HFD 510 Trade and generic names/dosage form: Velosulin BR (rDNA) Action: AP AE NA

Applicant Novo Nordisk Therapeutic Class 35

Indication(s) previously approved _____
Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application For use in external infusion pumps (For supplements, answer the following questions in relation to the proposed indication.)

1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.
2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.
3. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.
- a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
- b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
- c. The applicant has committed to doing such studies as will be required.
- (1) Studies are ongoing,
- (2) Protocols were submitted and approved.
- (3) Protocols were submitted and are under review.
- (4) If no protocol has been submitted, attach memo describing status of discussions.
- d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
4. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.
5. If none of the above apply, attach an explanation, as necessary.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

/s/  Supervisor
MD OFFICER _____ 4/26/99
Signature of Preparer and Title Date

cc: Orig NDA/PLA/PMA # _____
HF _____ /Div File
NDA/PLA Action Package
HFD-006/ SOImstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised 3/12/97)

BEST POSSIBLE COPY



Memorandum

Date: 4/26/99

/s/

From: Saul Malozowski
Acting Medical Team Leader

Subject: Velosulin BR (rDNA); NDA 21028 Pediatric Labeling

To: Solomon Sobel
Division Director, DMEDP

We have not received information to adequately label this product for its use in pediatric populations. Children hardly use insulin pumps. Insulin pumps have been successfully used, however, in adolescents but we do not have any information about pump use for this particular product. There is no reason to believe that the behavior of this formulation when used by a teenager will be different from any other populations. In addition, the target market will probably be quite small, making the feasibility of these studies dubious.

APPEARS THIS WAY ON ORIGINAL

Debarment Statement

In accordance with the requirements of the Generic Drug Enforcement Act of 1992, Novo Nordisk 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.



Barry Reit, Ph.D.
Vice President
Regulatory Affairs

22-July-1998
Date

Memorandum

July, 9 1999

To: the File NDA 21-028 Velosulin BR [Buffered human insulin (rDNA origin)]/

From: Solomon Sobel M.D. /S/ [redacted] Director Division of Metabolic and Endocrine Drugs

Subject: Approval of NDA

This NDA is for an insulin which is bioequivalent to another insulin (semisynthetic Velosulin BR) but is produced by a recombinant DNA process. Under our current regulation this change in manufacturing process, requires a submission under an NDA. The sponsor has performed a bioequivalence study in which bioequivalence was demonstrated.

In addition, a clinical study (Study 009) was done. This was an eight week study of cross-over design. In this study there were some small differences demonstrated in glucodynamic response which we do not consider significant. Overall, the average daily insulin dosage requirement remained the same for patients who were changed from rDNA to semisynthetic and vice versa. However there was evidence for a period effect. Those changed from rDNA in the 1st period to semisynthetic in the 2nd period had an increase in dosage in the 2nd period and those changed from semisynthetic in the 1st period to rDNA in the 2nd period had a decrease in daily dosage. However, when averaged out over both periods the daily dosage requirement was the same for the rDNA and the semisynthetic product.

No evidence of antibody formation to the rDNA product was noted over the duration of Study 009.

Although, the statistician has stated in his review that study 009 does not offer evidence for equivalence of rDNA to semisynthetic product, neither (he said) does it contradict the equivalence. The statistician points out issues of study design which may have produced this ambiguity.

The chemists found, from their standpoint, that this NDA may be approved.

Assay by [redacted] found the potency to comply with the specified range (95-105 U/ml)

The weight of evidence, particularly the clear pharmacokinetic bioequivalence, leads us to conclude that this rDNA product will behave identically to the semisynthetic one.

We do not believe that further clinical studies are needed.

Conclusion: The Division recommends approval for this NDA .

/S/ [redacted]

cc:OrigNDA 21-028
HFD-510/DivFile
HFD-510/JRhee

BEST POSSIBLE COPY