

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-172

Administrative Documents

INFORMATION ABOUT PATENTS RELATING TO BIPHASIC INSULIN ASPART

The patents mentioned below are the known U.S. patents which claim Biphaic Insulin Aspart. The patents belong to the company Novo Nordisk A/S, DK-2880 Bagsvaerd, Denmark. The applicant of the present New Drug Application, Novo Nordisk Pharmaceuticals, Inc., 100 Overlook Center, Suite 200, Princeton, New Jersey 08540, is a subsidiary of Novo Nordisk A/S.

The following U.S. patents are:

- **U.S. Patent No.: 5,618,913**
Expiration date: April 8, 2014
Type of patent: drug substance and drug product
Owner: Novo Nordisk A/S

- **U.S. Patent No.: 5,547,930**
Expiration date: September 28, 2013
Type of patent: drug product
Owner: Novo Nordisk A/S

- **U.S. Patent No.: 5,840,680**
Expiration date: September 28, 2013
Type of patent: drug product and method of use
Owner: Novo Nordisk A/S

- **U.S. Patent No.:** 5,834,422
Expiration date: September 28, 2013
Type of patent: drug product and method of use
Owner: Novo Nordisk A/S

- **U.S. Patent No.:** 5,948,751
Expiration date: June 19, 2017
Type of patent: drug product
Owner: Novo Nordisk A/S

U.S. agent authorized to receive notice of patent certification:

Steve T. Zelson
Director of Corporate Patents
Novo Nordisk of North America, Inc.
405 Lexington Avenue
Suite 6400
New York, N.Y.
NY 10174-6401

**APPEARS THIS WAY
ON ORIGINAL**

DECLARATION CONCERNING

U.S. PATENT NOS. 5,618,913; 5,547,930; 5,840,680; 5,834,422 and 5,948,751

The undersigned declares that U.S. Patent Nos. 5,618,913; 5,547,930; 5,840,680; 5,834,422 and 5,948,751 cover the formulation, composition and/or method of use of biphasic insulin aspart.

This product is the subject of this application for which approval is being sought.

Signed 2ND day of December, 1999

A handwritten signature in black ink, appearing to read "Steve T. Zelson", written over a horizontal line.

Steve T. Zelson

Director of Corporate Patents
Novo Nordisk of North America, Inc.

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Exclusivity Checklist

NDA: 21-172
Trade Name: NovoLog Mix 70/30
Generic Name: 70% insulin aspart protamine [rDNA origin] suspension and 30% insulin aspart [rDNA origin] solution)
Applicant Name: Novo Nordisk Pharmaceuticals, Inc.
Division: Division of Metabolic and Endocrine Drug Products, HFD-510
Project Manager: Julie Rhee, 7-6424
Approval Date:

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 questions about the submission.

a. Is it an original NDA?	Yes	X	No	
b. Is it an effectiveness supplement?	Yes		No	X
c. If yes, what type? (SE1, SE2, etc.)				
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.

Explanation:

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:

Explanation:

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?				

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

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?	Yes		No	x
If yes, NDA #				

Drug Name:

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

3. Is this drug product or indication a DESI upgrade?	Yes		No	x
IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).				

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

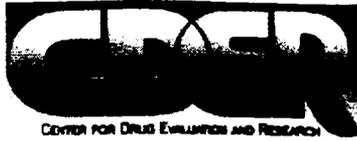
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.	Yes		No	
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,	Yes		No	

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.				
If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).				
Drug Product:				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				
2. Combination product.	Yes		No	
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 <u>any one</u> 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).				
Drug Product				
NDA #				
Drug Product				
NDA #				
Drug Product				
NDA #				
IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. 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.				
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. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.				
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	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>
If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCKS.				
Basis for conclusion:				
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	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
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	<input type="checkbox"/>	No	<input type="checkbox"/>
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	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
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:				
Investigation #1, Study #: 038				
Investigation #2, Study #:				
Investigation #3, Study #:				
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	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
Investigation #2	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>
Investigation #3	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>
If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
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	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
Investigation #2	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>
Investigation #3	Yes	<input type="checkbox"/>	No	<input type="checkbox"/>
If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation				

was relied on:			
Investigation #1 -- NDA Number			
Investigation #2 -- NDA Number			
Investigation #3 -- NDA Number			
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"):			
Investigation #1 038			
Investigation #2			
Investigation #3			
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 #1 038	Yes	<input checked="" type="checkbox"/>	No
IND#: 			
Explain:			
Investigation #2	Yes		No
IND#: 			
Explain:			
Investigation #3	Yes		No
IND#: 			
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		No
IND#: 			
Explain:			
Investigation #2	Yes		No
IND#: 			
Explain:			
Investigation #3	Yes		No
IND#: 			
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
			<input checked="" type="checkbox"/>
If yes, explain:			



PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number: N 021172
Trade Name: 70/30 (BIPHASIC INSULIN ASPART 30)
Generic Name: BIPHASIC INSULIN ASPART 30
Supplement Number: 000 **Supplement Type:** N
Dosage Form:
Regulatory Action: AE **Action Date:** 11/15/00
COMIS Indication: TREATMENT OF DIABETES MELLITUS

Linked to COMIS

Indication #1: NovoLog Mix 70/30 is indicated for the treatment of patients with diabetes mellitus for the control of hyperglycemia.

Label Adequacy: Other - see comments
Formulation Needed: No new formulation is needed
Comments (if any)

Lower Range	Upper Range	Status	Date
0 years	0 years	Waived	

Comments: Most pediatric patients with diabetes, especially those who are prepubescent, are type 1 patients. Fixed ratio and BID dosing cannot provide the tight control needed to avoid the long-term complications of diabetes. Even in post-pubertal patients with diabetes primarily linked to childhood obesity, tight control is likely to be important because of the expected long duration of disease. Such BID dosing regimens with fixed ratios are unlikely to provide tight control and minimize insulin-hunger that could foster progressive obesity.

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This page was last edited on 10/11/01



 Signature

 10-11-01
 Date

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PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA Number: 021172 Trade Name: _____, 70/30(BIPHASIC INSULIN ASPART 30)
 Supplement Number: 000 Generic Name: BIPHASIC INSULIN ASPART 30
 Supplement Type: N Dosage Form:
 Regulatory Action: OP COMIS Indication: TREATMENT OF DIABETES MELLITUS
 Action Date: _____ Primary: 10/22/00
 Secondary: 12/22/00

Indication # 1 NovoLog Mix 70/30 is indicated for the treatment of patients with diabetes mellitus for the control of hyperglycemia.
 Label Adequacy: Other - See Comments
 Formulation Needed: NO NEW FORMULATION is needed
 Comments (if any): Approvable

<u>Lower Range</u>	<u>Upper Range</u>	<u>Status</u>	<u>Date</u>
0 years	0 years	Waived	

Comments: Most pediatric patients with diabetes, especially those who are prepubescent, are type 1 patients. Fixed ratio and BID dosing cannot provide the tight control needed to avoid the long-term complications of diabetes. Even in post-pubertal patients with diabetes primarily linked to childhood obesity, tight control is likely to be important because of the expected long duration of disease. Such BID dosing regimens with fixed ratios are unlikely to provide tight control and minimize insulin-hunger that could foster progressive obesity.

This page was last edited on 9/21/00

Signature - _____

Date

9-21-00

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43 pages redacted from this section of
the approval package consisted of draft labeling

NDA 21-172
Biphasic insulin aspart 30
Debarment Statement

Date:

December 1999 **Novo Nordisk**

Debarment Statement

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 submission.



Barry Reit, PhD
Vice President
Regulatory Affairs

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CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) 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). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See Exhibit A of Sept 23, 1999	
	45 centres in Europe	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Anders Lindholm, MD, PhD	International Development Manager
FIRM/ORGANIZATION	
Novo Nordisk A/S	
SIGNATURE	DATE
Anders Lindholm	23 Sept -99

Paperwork Reduction Act Statement

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. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research

DATE: November 1, 2001

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-172
NovoLog Mix 70/30 (70% insulin aspart protamine suspension and 30% insulin aspart injection)

SUBJECT: NDA review issues and action

Background

This is the second review cycle for this NDA. The product proposed for marketing contains 30% soluble insulin aspart (Iasp) and 70% protamine Iasp (70/30). Iasp is currently marketed under NDA 20-986 as Novolog. It is a rapid-acting insulin analogue that differs from human insulin by a single amino acid substitution (asp for pro) at position 28 of the B-chain. As such, it does not form hexamers in solution and so is more rapidly absorbed after subcutaneous injection than is regular human insulin.

This application received an "approvable" action on November 7, 2000, citing the absence of PK/PD data comparing 70/30 to Novolog 50/50 (a mix not yet marketed). These data were not yet available at the time of the submission, at the request of the Division, during the first review cycle of data from two arms (Novolog 70/30 and Novolog) of study number 1086, a euglycemic clamp study in normal volunteers. Those data, specific requested analyses, and information on the insulin antibody studies conducted as part of this NDA have now been submitted and reviewed. In addition, 5 minor CMC deficiencies have been addressed by the sponsor.

The following background information and discussion is excerpted from my memorandum of November 6, 2000:

The development of the current proposed product and review of the application were undertaken in the context of the Agency's unofficial guidance on fixed-dose combination insulin products. Specifically, the Agency has required pharmacokinetic and pharmacodynamic data to show that, by weight of evidence, the combination product is different from its components individually and is also different from other combinations currently available. Though not stated in our unofficial guidance, other combinations apt to be proposed for marketing or likely to be used by patients mixing their own rapid and long-acting insulins may also be relevant comparators. For reasons that are thus self-evident, the comparisons to other combinations in the same family should, at a minimum, include those mixes expected to be closest in PK/PD behavior to the new product. This is in order to avoid approval and marketing of nominally distinct but truly duplicate

NDA 21-172, response to AE
NovoLog Mix 70/30
Insulin aspart
11/01/01

products from the same manufacturer. It therefore follows that, where possible, the new product should be studied so as to provide "bracketing" data with these closest comparators. Thus, in the present case, the proposed 70/30 mix should be compared both to the sponsor's 50/50 mix

A logical substitute would be NPH human insulin (Novolin NPH). However, as discussed below, Iasp 70/30 has already been demonstrated to be distinct pharmacokinetically from HI 70/30 and thus is assumed to be pharmacokinetically distinct from NPH human insulin.

"Different" has been defined as a minimum 20% difference in any of a number of parameters related to insulin kinetics or glucose utilization dynamics. It is important to note that the requirement for demonstration of such differences avoids a requirement for clinical data (trials measuring HbA1c). The efficacy and safety of insulin are well established. Antibody data have been included in the current application and are particularly relevant to the insulin analogues, such as Iasp. It is also important to note that inferences of clinical superiority of one product over another cannot be made based upon comparative PK/PD data. From the standpoint of labeling and promotion, the importance of the comparative studies lies in providing adequate information for prescribers to make informed decisions on the utility of the various insulin products as potential convenience products in patients otherwise mixing their own rapid and intermediate or long-acting insulins.

The sponsor submitted results from 4 PK/PD studies as follows:

<i>Trial</i>	<i>Subjects</i>	<i>Design features</i>
031: PK	Healthy volunteers	Single dose crossover, fasting, Iasp 70/30 vs. HI 70/30
033: PK/PD	Healthy volunteers	Single dose crossover, euglycemic clamp, Iasp 70/30 vs. HI 70/30
046: PK/PD	Type 2 DM	Multiple doses, non-fasting
1086: PK/PD	Healthy volunteers	Single dose, 4-way crossover, euglycemic clamp, Iasp 70/30 vs. Iasp vs. Iasp 50/50 vs. Iasp 30/70 (data submitted only for first two treatments)

In addition, data from a three month efficacy and safety study (038) in type 1 and type 2 DM treated with Iasp 70/30 or HI 70/30 were submitted.

Medical/Biopharmaceutics

Study 1086 was a 4-way crossover clamp study that included single-dose treatments with Iasp 70/30, Iasp, and Iasp 50/50, and Iasp 30/70. This study employed the to-be-marketed formulation of Iasp 70/30. The complete insulin PK and glucose utilization (PD) data from this study have now been reviewed.

Dr. Koller and Dr. Sun (OCPB) have recommended approval based on the finding of approximate 20% differences in Cmax and AUC for insulin PK and glucose utilization over time between 70/30 and 50/50.

No issues were raised by review of the antibody data in this submission.

A few points that relate to labeling are worth making:

While this drug product is not manufactured by

[nevertheless, the 70/30 mix does, effectively, have two physical-chemical phases. This is evidenced by the PK characteristics of the product, which shows a rapid absorption (and therefore onset of insulin action) attributable to fully soluble Iasp and a prolonged "tail" of assayable insulin aspart with a prolonged duration of action as demonstrated in the clamp studies (up to 24 hours).]

This product does not, strictly speaking, exhibit biphasic pharmacokinetics and dynamics, however, its overall PK/PD characteristics are clearly explained by the two, differentially absorbed, components of the mix.

With the above in mind, a description of the salient characteristics of PK and PD are clearly warranted in labeling, and to the extent that an understanding of these characteristics is important to the safe and effective use of the product, these features (specifically the rapid onset of action due to the Novolog component) should be reiterated in sections addressing specific precautions in use (e.g., special populations).

The second important point is that no clinical studies have been conducted with this product, or for that matter with other sponsors' insulin mixes, that speak to superior efficacy or safety compared to mixes in the same or different product lines. In the case of 70/30, the clinical comparison to Novolin 70/30 (human insulin mix) was notable for the relative poor control in both treatment groups and the minimal reductions in HbA1c from baseline that were indistinguishable across the treatment arms. With this in mind, and considering other significant limitations associated with the use of fixed ratio insulin mixes, we have added language to Clinical Pharmacology and Precautions addressing these facts and making clear that clinical significance of the differences in PK parameters between the different insulins studied has not been determined.

Finally, consistent with the labeling for Humalog (Lilly's rapid-acting insulin analogue), I have accepted a proposed table in the Clinical Studies section that summarizes end-of-study glucose parameters in the 3-month study in Type 1 and Type 2 patients comparing treatment with NovologMix 70/30 to that with Novolin 70/30. In essence, the table shows no difference in HbA1c between treatment groups for either population at the end of the treatment period, slightly higher FBG in the Type 1 patients treated with NovologMix 70/30, and minor (10-15 mg/dL) reductions in 1.5 hour post-breakfast and post-dinner glucose levels in the patients treated with twice daily injections of NovologMix 70/30 as compared to Novolin 70/30. This is followed by

NDA 21-172, response to AE
NovoLog Mix 70/30
Insulin aspart
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a disclaimer stating that the significance, with respect to long-term clinical sequelae of diabetes, of the differences in post-prandial hyperglycemia have not been established.

Pharmacology/Toxicology

This product has been labeled Pregnancy Category C. The effects on fetal development as seen in preclinical studies with Novolog are likely related to the pharmacologic effects of insulin, rather than true toxicity. Nevertheless, because of these findings, because of the absence of clinical trials in pregnant women, and because fixed ratio combination insulins are less than ideal for use in pregnancy, the labeling recommends use in pregnancy "only if benefits outweigh risks to the fetus" (from 21 CFR 201.57).

Chemistry/ Microbiology

The chemistry, manufacturing, and controls are satisfactory and the application is approvable from the standpoint of ONDC. The deficiencies in the original action letter have been addressed. The site inspections were all acceptable.

A categorical exclusion from the environmental assessment was claimed by the sponsor and accepted by the Agency.

The sterility data are satisfactory and support approval.

The February 9, 2001 complete response to the Approvable letter contained information on a fourth package size proposed for Novolog 70/30. This was not initially noted as it had not been proposed in the original NDA. Dr. Komanduri has reviewed the CMC information for the 3 ml FlexPen prefilled syringe and finds it approvable. As Dr. Koller has not been able to review and comment on the labeling regarding safe use of this device, this will not be approved at this time. The sponsor has been asked to submit a packaging supplement to the NDA which will be reviewed after approval of the original NDA.

DSI

After discussion with the team and with Dr. Jenkins, I have decided that DSI inspections of the analytical and euglycemic clamp study sites in Europe related to Study 1086 are not required.

_____ Briefly, there are no compelling reasons to question the overall integrity of the data from this study. The findings with regard to PK/PD relationships across the arms of the study are as expected and there are no irregularities in the data submitted that would support a specific need to audit either the study site or the analytical site.

Financial disclosure

The financial disclosure information is in order. The sponsor has certified that no investigator received outcome payments, that no investigator disclosed a proprietary interest in the product or an equity interest in the company, and that no investigator was the recipient of significant payments of other sorts.

OPDRA/nomenclature

The sponsor has agreed to change the proprietary name from the original _____ 70/30 to NovoLog Mix 70/30 consistent with the recommendation from OPDRA.

Recommendation

This application may be approved pending agreement on final labeling.

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this page is the manifestation of the electronic signature.**

/s/

David Orloff
11/1/01 07:03:21 PM
MEDICAL OFFICER

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MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

Date: August 31, 2000
From: Lee-Ping Pian, Ph.D. (HFD-715)
Subject: NDA 21-172 Biphasic Insulin Aspart 30
Submission dated: December 17, 1999
To: File (NDA 21-172)

Biphasic Insulin Aspart 30 (BIAsp 30) is a premixed insulin with a rapid onset and an intermediate duration of action for the treatment of diabetes mellitus.

ANA/DCD/038/D, UK was an open-label, randomized, parallel group, multicenter, multinational efficacy and safety study of BIAsp 30 or biphasic human insulin 30/70 (BHI 30) as meal related insulin in a twice daily regimen in Type 1 and Type 2 diabetic patients for 12 weeks. The primary objective of the study was to demonstrate non-inferiority of BIAsp 30 to BHI 30 with respect to HbA_{1c} measurement after 12 weeks of treatment.

A total of 294 patients were randomized, 143 to the BIAsp 30 group and 151 to the BHI 30 group. Three patients randomized to the BHI 30 group were not exposed to the trial products. Of the 291 exposed patients, 279 were included in the intent-to-treat (ITT) population with 12 patients excluded for no postbaseline measurements. A total of 260 patients were included in the per protocol (PP) population which excluded patients with protocol violation or not completing the trial. For the primary efficacy outcome, HbA_{1c}, the study reported 275 patients in the ITT population and 259 in the PP population (pp140, 141, Vol. 50).

The analysis of covariance on HbA_{1c} at month 6 with baseline HbA_{1c} as a covariate and a factor for treatment was performed on both the ITT and PP populations. The — % upper limit of the 95% confidence interval for the difference between treatments was less than the non-inferiority margin of — % for the ITT and the PP populations. The — % non-inferiority margin was prespecified in studies of NDA 20-986 for the NovoLog insulin aspart as well as in this study protocol. Table 1 displays this reviewer's ANCOVA results for both the ITT and PP populations. The number of patients in the analysis was 276 for the ITT population from the dataset provided by the sponsor.

Table 1 ANCOVA results at Week 12 for HbA_{1c}

	n	BIAsp 30 Mean (SE)	n	BHI 30 Mean (SE)	BIAsp 30 – BHI 30 Mean (95% CI)	p-value
ITT						
Baseline	133	8.23 (0.10)	143	8.27 (0.10)		
Week 12		8.13 (0.06)		8.12 (0.06)	+0.015 (-0.14, 0.17)	0.85
PP						
Baseline	124	8.24 (0.11)	135	8.22 (0.10)		
Week 12		8.10 (0.06)		8.12 (0.06)	-0.012 (-0.17, 0.15)	0.88

In conclusion, the BIAsp 30 was not inferior to BHI 30 in the primary efficacy outcome of HbA_{1c} at month 6.

/S/

Lee-Ping Pian, Ph.D.
Mathematical Statistician

Concur: Dr. Sahlroot

/S/ 9/1/00

cc:

- Archival NDA 21-172
- HFD-510
- HFD-510/SMalozowski, EKoller, JRhee
- HFD-715/Division file, TSahlroot, LPian

**APPEARS THIS WAY
ON ORIGINAL**

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research

DATE: November 6, 2000

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-172
NovoLog Mix 70/30 (70% insulin aspart protamine suspension and 30% insulin aspart injection)

SUBJECT: NDA review issues and action

Background

The product proposed for marketing contains 30% soluble insulin aspart (Iasp) and 70% protamine Iasp and is designed to provide both rapid-acting and intermediate-acting insulin-mediated control of blood glucose in diabetes mellitus. This memo will hereafter refer to the proposed product as Iasp 70/30. Insulin aspart (X-14) is currently marketed under NDA 20-986. It is a rapid-acting insulin analogue that differs from human insulin by a single amino acid substitution (asp for pro) at position 28 of the B-chain. The development of the current proposed product and review of the application were undertaken in the context of the Agency's unofficial guidance on fixed-dose combination insulin products. Specifically, the Agency has required pharmacokinetic and pharmacodynamic data to show that, by weight of evidence, the combination product is different from its components individually and is also different from other combinations currently available. Though not stated in our unofficial guidance, other combinations apt to be proposed for marketing or likely to be used by patients mixing their own rapid and long-acting insulins may also be relevant comparators. For reasons that are thus self-evident, the comparisons to other combinations in the same family should, at a minimum, include those mixes expected to be closest in PK/PD behavior to the new product. This is in order to avoid approval and marketing of nominally distinct but truly duplicate products from the same manufacturer. It therefore follows that, where possible, the new product should be studied so as to provide "bracketing" data with these closest comparators. Thus, in the present case, the proposed 70/30 mix should be compared both to the sponsor's 50/50 mix

A logical substitute would be NPH human insulin (Novolin NPH). However, as discussed below, Iasp 70/30 has already been demonstrated to be distinct pharmacokinetically from HI 70/30 and thus is assumed to be pharmacokinetically distinct from NPH human insulin.

"Different" has been defined as a minimum 20% difference in any of a number of parameters related to insulin kinetics or glucose utilization dynamics. It is important to note that the requirement for demonstration of such differences avoids a requirement for clinical data (trials measuring HbA1c). The efficacy and safety of insulin are well established. Antibody data have

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been included in the current application and are particularly relevant to the insulin analogues, such as Iasp. It is also important to note that inferences of clinical superiority of one product over another cannot be made based upon comparative PK/PD data. From the standpoint of labeling and promotion, the importance of the comparative studies lies in providing adequate information for prescribers to make informed decisions on the utility of the various insulin products as potential convenience products in patients otherwise mixing their own rapid and intermediate or long-acting insulins.

The sponsor submitted results from 4 PK/PD studies as follows:

Trial	Subjects	Design features
031: PK	Healthy volunteers	Single dose crossover, fasting, Iasp 70/30 vs. HI 70/30
033: PK/PD	Healthy volunteers	Single dose crossover, euglycemic clamp, Iasp 70/30 vs. HI 70/30
046: PK/PD	Type 2 DM	Multiple doses, non-fasting
1086: PK/PD	Healthy volunteers	Single dose, 4-way crossover, euglycemic clamp, Iasp 70/30 vs. Iasp vs. Iasp 50/50 vs. Iasp 30/70 (data submitted only for first two treatments)

In addition, data from a three month efficacy and safety study (038) in type 1 and type 2 DM treated with Iasp 70/30 or HI 70/30 were submitted.

Medical/Biopharmaceutics

The pivotal PK and PK/PD studies, 031 and 033, did not employ the to-be-marketed formulation of Iasp 70/30. However, the OCPB reviewer has commented that insofar as "... this drug product is for s.c. injection, with the small changes in formulation [relative to the to-be-marketed product] it seems unlikely that the above PK and PD study conclusions would be different."

The results of these studies demonstrate that compared to HI 70/30, Iasp 70/30 has a more rapid absorption with a shorter T_{max}, a markedly higher C_{max} (50% higher than HI 70/30), and an insulin AUC from 0-90 minutes approximately double the comparator. These data support pharmacokinetic distinctiveness from the comparator.

Dr. Koller has reviewed the clinical study (038). This trial employed the to-be-marketed formulation. This trial enrolled approximately 100 patients with type 1 DM and about 180 patients with type 2 DM. Each group was randomized 1:1 to treatment with either Iasp 70/30 or human insulin (HI) 70/30 before breakfast and dinner. Doses were adjusted in order to achieve glycemic control while avoiding hypoglycemia. The trial lasted 3 months. Results for change from baseline in HbA_{1c} showed no significant between group differences. Notably, mean HbA_{1c} levels did not fall significantly during the trial, suggesting that use of the fixed-combination insulin products provides less than ideal glycemic control. There were trends toward higher total daily doses of insulin used in patients, whether type 1 or type 2, treated with Iasp 70/30. In addition, the levels of cross-reacting anti-insulin antibodies were substantially

higher in the Iasp-treated groups than in the HI-treated groups. While the patients with high levels of antibodies did not necessarily require higher doses of insulin in this study, the clinical significance of the antibody finding is not known. The finding is consistent with the results of the original NDA studies for Iasp, according to Dr. Koller's review. In short, no clinical superiority of Iasp 70/30 over the comparator was demonstrated in this study. I concur with Dr. Koller that, as such, none should be implied in labeling, regardless of the findings from the PK studies.

Study 1086 was a 4-way crossover clamp study that included single-dose treatments with Iasp 70/30, Iasp, and Iasp 50/50, and Iasp 30/70. This study employed the to-be-marketed formulation of Iasp 70/30. Of note, only the data for the first two treatments were submitted. As such, the application contains only interim or preliminary data from this study. From our standpoint, the report is incomplete. Indeed, based upon this fact, we have asked DSI to delay any audit of this trial until all of the data from it are submitted to the agency for review. The sponsor contends that the data from the other comparators are not relevant to the current application. Consistent with the discussion in the Introduction section, above, the data as submitted do indeed neglect critical comparators necessary to distinguish this product from other mixes marketed _____ or likely to be utilized by patients. Specifically, in this case, it is not sufficient to compare the new product to its rapid-acting component alone. It is important, in order to distinguish it from other products in the Iasp family, to "bracket" the PK/PD data for Iasp 70/30 with data from comparative studies with Iasp 50/50. As in Introduction, a comparison to NPH human insulin is not warranted in light of the results of studies 031 and 033, above.

Study 046 was not reviewed.

Pharmacology/Toxicology

Extensive pre-clinical toxicology is not required. Acute toxicity in animals is attributable to hypoglycemia. Local cutaneous toxicity was unremarkable. The product is antigenic in rabbits insofar as it differs by two amino acids from rabbit insulin. Labeling changes have been conveyed to the sponsor.

Chemistry/ Microbiology

The chemistry, manufacturing, and controls are satisfactory and the application is approvable from the standpoint of ONDC, pending satisfactory response to certain deficiencies identified. These were conveyed to the sponsor on September 27, 2000.

The site inspections were all acceptable.

A categorical exclusion from the environmental assessment was claimed by the sponsor and accepted by the Agency.

The sterility data are satisfactory and support approval.

DSI

No DSI audit was performed as the sponsor submitted only interim data from the pivotal 4-way crossover study conducted at the site in Germany. As such, since the Division was unable to review the complete data, the DSI audit was deferred until such time as the data are submitted or another adequate pivotal trial is conducted and reported to the Agency.

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Financial disclosure

The financial disclosure information is in order. The list of investigators at 45 European sites was provided. The sponsor has certified that no investigator received outcome payments, that no investigator disclosed a proprietary interest in the product or an equity interest in the company, and that no investigator was the recipient of significant payments of other sorts.

OPDRA/nomenclature

The sponsor has agreed to change the proprietary name from the original ~~NovoLog Mix 70/30~~ 70/30 to NovoLog Mix 70/30 consistent with the recommendation from OPDRA.

Recommendation

This application is approvable. However, the sponsor must address the deficiencies discussed above and included in the ONDC review. Final labeling will be negotiated at that time.

CC:

HFD-510

NDA 21-172 Arch

APPEARS THIS WAY
ON ORIGINAL

/s/

David Orloff
11/8/00 05:37:01 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL