CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-172

Chemistry Review(s)

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA 21-172 **CHEMISTRY REVIEW: #2** **DATE REVIEWED:** 26th Sept-2001

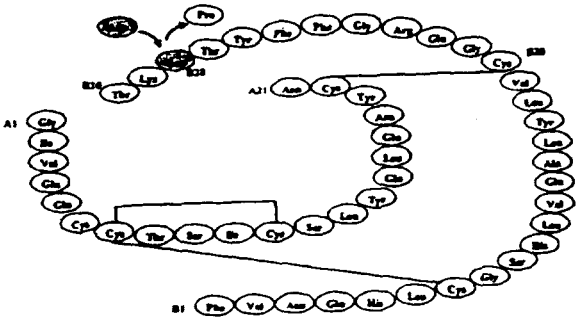
SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	22nd-Dec-1999	23rd-Dec-1999	1st-Mar-2000
Amendment	9th-Feb-2001	12th-Feb-2001	13th-Feb-2001

NAME & ADDRESS OF APPLICANT: Novo Nordisk pharmaceuticals, Inc.,
Suite 200,
100, Overlook Center,
Princeton, NJ 08540-7810

DRUG PRODUCT NAME

Proprietary:	____ 70/30(70% protamine suspension and 30% injection)
Nonproprietary/Established/USA username (or equivalent):	Biphasic Insulin Aspart 30 (rDNA origin)
Code Name/#:	
Chem.Type/Ther.Class:	Long acting Insulin analog
ANDA Suitability Petition / DESI / Patent Status:	N/A
PHARMACOLOGICAL CATEGORY/INDICATION:	Treatment of diabetes mellitus
DOSAGE FORM:	sterile parenteral suspension
STRENGTHS:	100IU/ml
ROUTE OF ADMINISTRATION:	Injection
SPOTS:	Yes__X_____ No_____
DISPENSED:	_X_ Rx __ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
Molecular weight: 5825.8g/mol
Empirical Formula: $C_{256}H_{381}N_{65}O_{79}S_6$



SUPPORTING DOCUMENTS:

RELATED DOCUMENTS (if applicable): None

CONSULTS: None.

REMARKS/COMMENTS:

This amendment dated 9th Feb-2001, was submitted in response to the CMC comments that were sent to the sponsor based on the primary review of the original submission. This amendment also contained the stability commitment for the first three commercial batches of biphasic Insulin aspart 30, 100U/ml for both 10 ml vial and 3 ml Cartridges (pages 329-330, vol.2). The stability protocol for the 3 mL cartridge was also submitted in this amendment. The amendment also includes the updated stability data for both Penfill 3 ml, and for 10 ml vial. Revised labeling is also submitted. These comprise the subject of this review.

70/30 is a sterile, neutral, biphasic suspension with of 30% soluble rapid acting insulin aspart and 70% protamine – bound insulin aspart crystals with disodium hydrogen phosphate mannitol and zinc and sodium chloride Phenol and meta cresol

Insulin aspart is homologous to human insulin, with aspartic acid substitution for amino acid proline at position B28. The intermolecular charge repulsion due to the substitution reduces the tendency of the insulin molecules to self-associate. The *in vitro* and *in vivo* potency studies have shown that insulin aspart is equipotent to human insulin on a molar basis. The molar potency of insulin aspart is defined as IU = nmol.

CONCLUSIONS & RECOMMENDATIONS:

The CMC responses submitted by the sponsor in this amendment are satisfactory and the application can be approved from Chemistry stand point,

Org. NDA # 21172

cc: HFD-510/Division File
HFD-510/PardhaK/SMooore/Rhee J
HFD-820/duffyE
R/D Init by: Team Leader

/S/

Komanduri Pardha, Review Chemist
filename: N#21172

AP

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Pardhasaradhi Komanduri
9/27/01 11:25:22 AM
CHEMIST

Stephen Moore
9/27/01 12:02:14 PM
CHEMIST

WITHHOLD 2 PAGE (S)

Comments faxed to Novo on 9/27/00

Rhee

SEP 21 2000

DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA 21-172 **CHEMISTRY REVIEW: #1** **DATE REVIEWED:** 16th -Sept-2000

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
Original	22nd-Dec-1999	23rd-Dec-1999	1st-Mar-2000
Amendment	19th-July-2000	20th-July-2000	25th-July-2000

NAME & ADDRESS OF APPLICANT: Novo Nordisk pharmaceuticals, Inc.,
Suite 200,
100, Overlook Center,
Princeton, NJ 08540-7810

DRUG PRODUCT NAME

Proprietary: ——— 70/30(70% protamine suspension and 30% injection)

Nonproprietary/Established/USAusername (or equivalent): Biphasic Insulin Aspart 30 (rDNA origin)

Code Name/#:

Chem.Type/Ther.Class: Long acting Insulin analog

ANDA Suitability Petition / DESI / Patent Status: N/A

PHARMACOLOGICAL CATEGORY/INDICATION: Treatment of diabetes mellitus

DOSAGE FORM: sterile parenteral suspension

STRENGTHS: 100IU/ml

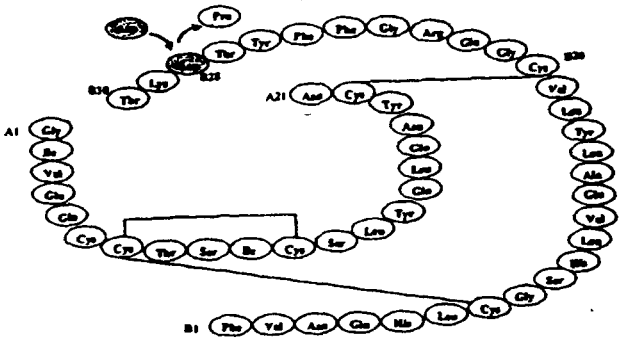
ROUTE OF ADMINISTRATION: Injection

DISPENSED: _X_ Rx __ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Molecular weight: 5825.8g/mol

Empirical Formula: $C_{256}H_{381}N_{65}O_{79}S_6$



SUPPORTING DOCUMENTS:

RELATED DOCUMENTS (if applicable): None

CONSULTS:

Both the Micro consult and the [redacted] device consult were submitted.

REMARKS/COMMENTS:

[redacted] 70/30 is a sterile, neutral, biphasic suspension with of 30% soluble rapid acting insulin aspart and 70% protamine – bound insulin aspart crystals with disodium hydrogen phosphate – [redacted] mannitol [redacted] and zinc and sodium chloride [redacted] Phenol and meta cresol [redacted]

Insulin aspart is homologous to human insulin, with aspartic acid substitution for amino acid proline at position B28. The intermolecular charge repulsion due to the substitution reduces the tendency of the insulin molecules to self-associate. The *in vitro* and *in vivo* potency studies have shown that insulin aspart is equipotent to human insulin on a molar basis. The molar potency of insulin aspart is defined as IU = [redacted] nmol.

This application is submitted for three packaging configurations of [redacted] 70/30.

Biphasic Insulin Aspart 30 10ml vial,
Biphasic Insulin Aspart 30 PenFill 3 ml cartridge,
Biphasic insulin Aspart 30 Prefilled 3ml syringe.

Subsequently, the sponsor has submitted a brief communication dated 19th-July-2000, with revised specifications for the container closure system for the above packaging configurations. This communication contained release specifications for 3 ml cartridge, 10 ml vial, [redacted]

The sponsor has indicated in the cover letter that the NovoPen 3 insulin pen that was approved earlier in reference to NDA 19938 (for Novolin R) will be used for Bipahsic Insulin Aspart 30 Penfill 3 ml Cartridges. After checking with the sponsor, it was confirmed that the [redacted] 3 ml pen injector with non-replaceable cartridges, which was also approved by FDA will be used for Biphasic Insulin Aspart 30 Prefilled 3 ml syringe.

Cross-reference was also made to NDA # 20986 for DMF document covering the [redacted] and for letters of authorization. Thus the DMF document for [redacted] for the drug product was not a part of this review.

The trade name submitted for the drug product was not accepted by OPDRA and the sponsor has been asked to provide a different trade name and an established name. See the labeling section of the chemistry review for details.

CONCLUSIONS & RECOMMENDATIONS:

The chemistry, manufacturing and controls (CMC) are satisfactory and the application is approvable from Chemistry stand point, pending satisfactory response to deficiencies (see draft Deficiency Letter).

Org. NDA # 21172

cc: HFD-510/Division File
HFD-510/PardhaK/SMooore/Rhee J
R/D Init by: Team Leader

/S/

Komanduri Pardha, Review Chemist
filename: N#21172

/S/
9/21/2000

APPEARS THIS WAY
ON ORIGINAL

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 21172/000**
Priority: **4S**
Org Code: **510**
Stamp: **22-DEC-1999** Regulatory Due: **22-OCT-2000**
Action Goal:
District Goal: **23-AUG-2000**
Applicant: **NOVO NORDISK PHARM**
100 OVERLOOK CENTER STE 200
PRINCETON, NJ 085407810
Brand Name: **[redacted] 70/30(BIPHASIC INSULIN ASPART 30**
Established Name:
Generic Name: **BIPHASIC INSULIN ASPART 30**
Dosage Form: **INJ (INJECTION)**
Strength: **100U/ML**

FDA Contacts:

H. RHEE	**(HFD-510)**	**301-827-6424**	**, Project Manager**
P. KOMANDURI	**(HFD-510)**	**301-827-6420**	**, Review Chemist**
S. MOORE	**(HFD-510)**	**301-827-6430**	**, Team Leader**

Overall Recommendation:

ACCEPTABLE on 13-MAR-2000 by M. GARCIA (HFD-322) 301-594-0095

Establishment: **9610095**
NOVO NORDISK A/S

BAGSVAERD, , DA

DMF No:
AADA No:

Profile: SVS
OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **22-FEB-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE LABELER**
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER

Establishment: **9610097**
NOVO NORDISK A/S

GENTOFTE, , DA

DMF No:
AADA No:

Profile: CTL
OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **10-MAR-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE OTHER TESTER**

Establishment: **9610699**
NOVO NORDISK A/S
HALLAS ALLE
KALUNDBORG 4400, , DA

DMF No:
AADA No:

Profile: SVS
OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **22-FEB-2000**

Responsibilities: **FINISHED DOSAGE LABELER**

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: **9613244**
NOVO NORDISK A/S
BERNNUM PARK, DK-3400
HILLEROED, , DA

DMF No:
AADA No:

Profile: **SVS** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **13-MAR-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE PACKAGER**

APPEARS THIS WAY
ON ORIGINAL

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application: **NDA 21172/000**
Stamp: **22-DEC-1999** Regulatory Due: **01-NOV-2001**
Applicant: **NOVO NORDISK PHARM**
100 OVERLOOK CENTER STE 200
PRINCETON, NJ 085407810

Priority: **4S** Org Code: **510**
Action Goal: District Goal: **23-AUG-2000**
Brand Name: **[redacted] 70/30(BIPHASIC INSULIN ASPART 30**
Established Name:
Generic Name: **BIPHASIC INSULIN ASPART 30**
Dosage Form: **INJ (INJECTION)**
Strength: **100U/ML**

FDA Contacts:

H. RHEE	**(HFD-510)**	**301-827-6424**	**, Project Manager**
P. KOMANDURI	**(HFD-510)**	**301-827-6420**	**, Review Chemist**
S. MOORE	**(HFD-510)**	**301-827-6430**	**, Team Leader**

Overall Recommendation:

ACCEPTABLE on 13-MAR-2000 by EGASM

Establishment: **9610095**
NOVO NORDISK A/S

BAGSVAERD, , DA

DMF No:
AADA No:

Profile: **SVS** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **22-FEB-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE LABELER**
FINISHED DOSAGE MANUFACTURER
FINISHED DOSAGE PACKAGER

Establishment: **9610097**
NOVO NORDISK A/S

GENTOFTE, , DA

DMF No:
AADA No:

Profile: **CTL** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **10-MAR-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Responsibilities: **FINISHED DOSAGE OTHER TESTER**

Establishment: **9610699**
NOVO NORDISK A/S
HALLAS ALLE
KALUNDBORG 4400, , DA

DMF No:
AADA No:

Profile: **SVS** OAI Status: **NONE**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **22-FEB-2000**

Responsibilities: **FINISHED DOSAGE LABELER**

ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: **9613244**
NOVO NORDISK A/S
BERNNUM PARK, DK-3400
HILLEROED, , DA

DMF No:
AADA No:

Profile: **SVS** OAI Status: **NONE** Responsibilities: **FINISHED DOSAGE PACKAGER**
Last Milestone: **OC RECOMMENDATION**
Milestone Date: **13-MAR-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**
