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

NDA #: 20-986
CHEMISTRY REVIEW #: 3
DATE REVIEWED: 15-SEP-1999

SUBMISSION TYPE | DOCUMENT DATE | CDER DATE
---|---|---
AMENDMENT | 26-AUG-1999 | 27-AUG-1999

NAME & ADDRESS OF APPLICANT:
Novo Nordisk Pharmaceuticals, Inc.
Suite 200, 100 Overlook Center
Princeton NJ 08450

DRUG PRODUCT NAME
Proprietary: NovoLog
Established: insulin aspart (rDNA origin)
Code Name/#: X-14
Chem Type/Ther.Class: 1-P

ANDA Suitability Petition / DESI / Patent Status:
The applicant holds US patent 5,618,913 which claims Insulin Aspart, and drug product containing Insulin Aspart.

PHARMACOLOGICAL CATEGORY/INDICATION: antihyperglycaemic

DOSAGE FORM: Solution for Injection
STRENGTHS: 100 U/mL
ROUTE OF ADMINISTRATION: sc injection
DISPENSED: X Rx ___ OTC
SPECIAL PRODUCTS: X Yes ___ No

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

SUPPORTING DOCUMENTS:
See review #1

RELATED DOCUMENTS:
IND

NDA: 20-986

APPEARS THIS WAY ON ORIGINAL
See review #1

REMARKS:

This review includes revised carton labels provided by the applicant in the two amendments dated 20 and 26 August, in response to the items noted in Chemistry Review #2. The applicant made the proposed changes, and the carton and vial and cartridge labels are now acceptable. The CDER Office of Compliance has, however, placed a "Withhold" recommendation for the facilities (see attached summary report dated 14-SEP-1999), and has also decided on re-inspection of the facilities after the firm has had time to implement changes based on the 483 items. After re-submission, the reviewing chemist will need to request re-inspection of the facilities.

CONCLUSIONS & RECOMMENDATIONS:

This application remains Approvable, due to the "Withhold" of a recommendation from the CDER Office of Compliance. No other CMC issues remain, however. The re-inspection request will need to be entered into EES upon receipt of the Applicant’s re-submission in response to the “Approvable” letter.

cc:
Org. NDA 20-966
HFD-510/Division File
HFD-510/WBerlin/date
HFD-510/CSO
HFD-510/SMoore
HFD-820/J Gibbs
R/D Init by: SMoore

William K. Berlin, Review Chemist

APPEARS THIS WAY ON ORIGINAL
DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA #: 20-986
CHEMISTRY REVIEW #: 2
DATE REVIEWED: 12-AUG-1999

SUBMISSION TYPE
ORIGINAL
AMENDMENT
AMENDMENT

DOCUMENT DATE
15-SEP-1998
27-MAY-1999
28-MAY-1999

CDER DATE
18-SEP-1998
26-MAY-1999
29-MAY-1999

NAME & ADDRESS OF APPLICANT:
Novo Nordisk Pharmaceuticals, Inc.
Suite 200, 100 Overlook Center
Princeton NJ 08450

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Proprietary: NovoLog
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Solution for Injection
STRENGTHS:
100 U/mL
ROUTE OF ADMINISTRATION:
sc injection
DISPENSED:
X Rx ___ OTC
X Yes ___ No

SPECIAL PRODUCTS:

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

In insulin aspart:

SUPPORTING DOCUMENTS:
See review #1

RELATED DOCUMENTS:
IND

NDA: 20-986

CONSULTS:

APPEARS THIS WAY
ON ORIGINAL
See review #1

REMARKS:

This review covers labeling and the applicant's response to the deficiencies noted in review #1, contained in the amendment dated 10-AUG-1999. They are acceptable. The Office of Compliance has not yet provided a recommendation for the manufacturing facilities, as of yet, however, and so the application remains "Approvable" based on CMC review.

CONCLUSIONS & RECOMMENDATIONS:

This application is 'Approvable' pending a recommendation from the CDER Office of Compliance for the Novo Nordisk manufacturing facilities and the applicant's inclusion of the minor labeling changes noted herein. There are no Phase IV chemistry commitments required of the applicant.

cc:
  Org. NDA 20-986
  HFD-510/Division File
  HFD-510/WBerlin/date
  HFD-510/CSO
  HFD-510/SMoore
  HFD-820/J.Gibbs
  R/D Init by: SMoore

filename:

William K. Berlin, Review Chemist

APPEARS THIS WAY
ON ORIGINAL
DIVISION OF METABOLISM AND ENDOCRINE DRUG PRODUCTS - HFD-510
Review of Chemistry, Manufacturing and Controls

NDA #: 20-986
CHEMISTRY REVIEW #: 1
DATE REVIEWED: 28-JUL-1999

SUBMISSION TYPE DOCUMENT DATE CDER DATE
AMENDMENT 21-JAN-1999 22-JAN-1999
AMENDMENT 29-JAN-1999 1-FEB-1999
AMENDMENT 19-FEB-1999 22-FEB-1999
AMENDMENT 15-MAR-1999 16-MAR-1999
AMENDMENT 8-JUN-1999 9-JUN-1999
AMENDMENT 10-JUN-1999 11-JUN-1999
AMENDMENT 15-JUN-1999 16-JUN-1999
AMENDMENT 21-JUN-1999 22-JUN-1999
AMENDMENT 13-JUL-1999 14-JUL-1999
AMENDMENT 21-JUL-1999 11-JUL-1999

NAME & ADDRESS OF APPLICANT:
Novo Nordisk Pharmaceuticals, Inc.
Suite 200, 100 Overlook Center
Princeton NJ 08450

DRUG PRODUCT NAME
Proprietary: NovoLog
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ANDA Suitability Petition / DESI / Patent Status:
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and drug product containing Insulin Aspart.

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DOSAGE FORM:
Solution for Injection
STRENGTHS:
100 U/mL
ROUTE OF ADMINISTRATION:
sc injection
DISPENSED:
X Rx __ OTC
X Yes __ No

SPECIAL PRODUCTS:

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

![Chemical Structure Diagram]

SUPPORTING DOCUMENTS:

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<th>Type/Number</th>
<th>Subject</th>
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<th>Status</th>
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</table>
1. Adequate control information

RELATED DOCUMENTS:
IND

NDA: 20-986

CONSULTS:
Labeling and Nomenclature consult: The applicant requested the name ______ in the original application. This name was found unacceptable to the LNC due to its suggestive nature and potential for confusion. The applicant then submitted the proposed name NovoLog. The LNC found this name to be acceptable (see attached copy of the LNC consult review).

REMARKS:
This application provides information for a recombinant insulin analogue, namely insulin aspart. The primary structure of the molecule is identical to that of human insulin with the exception of a Proline to Aspartic acid mutation at the __ position. This results in a _______ of the B-terminus that disrupts hexamer formation and lowers the binding constant. The functional result of this mutation is a more rapid PK (t_max) for the drug, compared to regular human insulin, after s.c. administration. The ______ system for this drug is functionally identical to that utilized by this manufacturer for insulin human, and is produced in the same S. cerevisiae cells.

The product is equipotent to human insulin on a molar basis, as demonstrated in two animal assays, as well as in clinical trials. The product will be distributed in a preserved aqueous formulation at 100 U/ml, as is standard for insulin drug products. Drug product presentations include the usual 10 ml vials, and cartridges of _______ for use in refillable or disposable insulin pens. The only drug product container/closure component provided for in this application that is not already in use with the applicant's other insulin products, is a _______ stopper to be used with both vials and cartridges. The product-contact surface of the new stopper is identical to that for the original stopper, however. The applicant has adopted the trade name of "NovoLog", and this proposal was found to be acceptable to the labeling and nomenclature committee (see attached consult review). The inspection recommendation for this application is pending, as an extensive 483 was issued during the inspection, and the applicant has yet to reply. The application has been reviewed by the CDER office of Microbiology staff, and it has been recommended for approval on the basis of assurance of sterility. The labeling review for this drug product will be deferred to chemistry review #2.

CONCLUSIONS & RECOMMENDATIONS:

This application is approvable pending the applicant's response to the items contained in the draft letter at the end of this review and pending a final recommendation by the Office of Compliance for the manufacturing facilities. The items in the Draft Letter should be forwarded to the applicant as soon as possible.

cc: Org. NDA #___
HFD-510/Division File
HFD-510/W/Beirut/date
HFD-510/CSO
HFD-510/Smab
HFD-102/JJGibbs [#1 only]
R/D Init by: SMab

(filename)

AE

/Signature/
William K. Berlin, Review Chemist

/Signature/
1/28/99
Draft