CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020918

CHEMISTRY REVIEW(S)

JUN 2 2 1998

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

NDA #: 20-918
CHEMISTRY REVIEW #: 3 **DATE REVIEWED:** 06-22-98

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	9-18-97	9-24-97	9-25-97
AMENDMENT	12-19-97	12-22-97	12-23-97
AMENDMENT	2-13-98	2-17-98	2-17-98
AMENDMENT	3-19-98	3-20-98	3-24-98
CORRESPONDENCE	4-20-98	4-21-98	4-29-98
AMENDMENT	5-22-98	5-26-98	5-29-98
AMENDMENT	6-10-98	6-11-98	6-11-98
AMENDMENT	6-16-98	6-17-98	6-17-98
AMENDMENT	6-22-98		

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

DRUG PRODUCT NAME

Proprietary:	GlucaGen®
Nonproprietary/Established/USAN:	Glucagon (rDNA origin) injection
Code Name/#:	Glucagon(ge)
Chem.Type/Ther.Class:	3 P

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

PHARMACOLOGICAL CATEGORY/INDICATION: Anti hypoglycemic agent

DOSAGE FORM: injection
STRENGTHS: 1 mg
ROUTE OF ADMINISTRATION: sc, im, iv injection
DISPENSED: _X_ Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
Using the standard, three-letter abbreviations, the primary structure of the protein is: H_2N-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Thr-Leu-Asp-Ser-Arg-Arg-Als-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met-Asn-Thr-OH. There are no disulfide bonds in the molecule. It has a molecular formula of $C_{153}H_{225}N_{43}O_{49}S$, and a molecular weight of 3483 Da.

SUPPORTING DOCUMENTS:
See Review #1

RELATED DOCUMENTS (if applicable):
(b)(4) [redacted]

CONSULTS:
Microbiology; CDER Labeling and Nomenclature Committee

REMARKS/COMMENTS:

This review covers the responses to a chemistry information request (b)(4) [redacted]
(b)(4) [redacted]

review of the Form 483 which was issued to the Sponsor after the prior approval inspection (PAI).

(b)(4) [redacted]

The Amendment of 6-16-98 contained updates to the NDA to reflect items where the actual process differed from that described in the NDA (b)(4) [redacted] and listed in the 483 which was issued to the sponsor on 3-5-98.

The Amendment of 6-22-98 (b)(4) [redacted] included the sponsor's reply to the Agency's request

(b)(4) [redacted]

CONCLUSIONS & RECOMMENDATIONS:

The Amendments provided to the original application have satisfied all of the chemistry requirements for the application, in terms of CMC review. The facilities for manufacturing have been inspected in support of this application and found to be acceptable as of 6-22-98 (b)(4) [redacted] This application is recomended for APPROVAL based on the satisfactory pre-approval inspection and the CMC review.

cc:
Org. NDA 20-918
HFD-510/Division File
HFD-510/WBerlin/SMoore
HFD-510/CSO/JRhee
R/D Init by: SMoore

/s/ [redacted]
William K. Berlin, Review Chemist

AP

/s/ [redacted]

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

NDA #: 20-918
CHEMISTRY REVIEW #: 2 **DATE REVIEWED:** 06-10-98

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	9-23-97	9-24-97	9-25-97
AMENDMENT	10-29-97	11-07-97	11-14-97
AMENDMENT	12-19-97	12-22-97	12-23-97
AMENDMENT	2-13-98	2-17-98	2-17-98
AMENDMENT	3-19-98	3-20-98	3-24-98
AMENDMENT	4-20-98	4-21-98	4-29-98
AMENDMENT	5-22-98	5-26-98	5-29-98

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

DRUG PRODUCT NAME
Proprietary: GlucaGen®
Nonproprietary/Established/USAN: Glucagon (rDNA origin) injection
Code Name/#: Glucagon(ge)
Chem.Type/Ther.Class: 3 P

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

PHARMACOLOGICAL CATEGORY/INDICATION: Anti hypoglycemic agent

DOSAGE FORM: injection
STRENGTHS: 1 mg
ROUTE OF ADMINISTRATION: sc, im, iv injection
DISPENSED: _X_ Rx ___ OTC

CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:
Using the standard, three-letter abbreviations, the primary structure of the protein is: H_2N-His-Ser-Gln-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Lys-Thr-Leu-Asp-Ser-Arg-Arg-Ala-Gln-Asp-Phe-Val-Gln-Trp-Leu-Met-Asn-Thr-OH. There are no disulfide bonds in the molecule. It has a molecular formula of $C_{153}H_{225}N_{43}O_{49}S$, and a molecluar weight of 3483 Da.

SUPPORTING DOCUMENTS:
See Reveiw #1

RELATED DOCUMENTS (If applicable):
(b)(4) [redacted]

CONSULTS:
Microbiology; CDER Labeling and Nomenclature Committee

REMARKS/COMMENTS:

This review covers the responses to a chemistry information request letter issued to the firm on the basis of Chemistry Review #1 (see FDA letter dated 3-4-98).

The amendment of 3-19-98 contains most of the responses to the chemistry comments from review #1, as well as the

sponsor's responses to the observations listed in the 483 from the prior approval inspection, for the convenience of the reviewer. The amendment of 4-20-98 contained a report on the (b)(4) and the corresponding antisera. The amendment of 5-22-98 contained updated stability data.

Two of the responses in the 3-19-98 amendment were not satisfactory, and the sponsor has been asked to clarify these two items. In addition, following a discussion with the field investigator, Joyce Bloomfield, it was decided to ask the sponsor to replace the term (b)(4) particluar on the relevant SOP's and Batch Records. Because the [redacted] application of the (b)(4) [redacted], at best. The investigator noted instances where such inaccurate termonology has led to compliance problems with other products. All three comments were forwarded to the sponsor by a telephone call (b)(4) [redacted]

CONCLUSIONS & RECOMMENDATIONS:

There remain compliance problems with two of the facilities, namely the (b)(4) [redacted] at Gentofte, and the analytical lab in Soborg. These facilities currentlly have a "Withold" recomendation under the establishment evaluation system file for this application. Therefore, based on CMC, this application may only be recommended as Approvable, pending satisfactory resolution of the compliance problems, and based on satisfactory answer of the three chemistry comments in this review. The three chemistry questions in this review were communicated to the sponsor via a telephone call with Mary Anne McElligot of Novo Nordisk, 6-10-98 at 2:00 pm (see attached record of telephone conversation).

~~APPEARS THIS WAY ON ORIGINAL~~ [redacted]

cc:
Org. NDA 20-918
HFD-510/Division File
HFD-510/WBerlin/SMoore
HFD-510/CSO/JRhee
R/D Init by: SMoore

/s/ [redacted]
William K. Berlin, Review Chemist

AE

filename: C:wpfiles\nda1998\20918\chemrev2.001

/s/ [redacted]

~~APPEARS THIS WAY ON ORIGINAL~~ [redacted]

~~APPEARS THIS WAY ON ORIGINAL~~ [redacted]

CMC comments faxed to Novo on 3/4/98

Rhee, J

MAR - 4 1998

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

NDA #: 20-918
CHEMISTRY REVIEW #: 1 **DATE REVIEWED:** 03-04-98

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	9-23-97	9-24-97	9-25-97
AMENDMENT	10-29-97	11-07-97	11-14-97
AMENDMENT	12-19-97	12-22-97	12-23-97
AMENDMENT	2-13-98	2-17-98	2-17-98

NAME & ADDRESS OF APPLICANT: Novo Nordisk, Pharmaceuticals Inc.
200 Overlook Center
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DRUG PRODUCT NAME
Proprietary: GlucaGen®
Nonproprietary/Established/USAN: Glucagon (rDNA origin) injection
Code Name/#: Glucagon(ge)
Chem.Type/Ther.Class: 3 P

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

PHARMACOLOGICAL CATEGORY/INDICATION: Anti hypoglycemic agent

DOSAGE FORM: injection
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SUPPORTING DOCUMENTS:

(b)(4) [redacted]

RELATED DOCUMENTS (if applicable):

(b)(4) [redacted]

NDA 20-918

CONSULTS:
The sponsor's proprietary name GlucaGen® was forwarded to the Labeling and Nomenclature Committee for comment (see attached copy of the committee's recomendation dated 2-23-98). The committee concluded that the name was unacceptable because of potential confusion with the USAN name Glucagon. However, approval of this application will provide for only the second manufacturer for this drug in the US. Secondly, the drug from both manufacturers is equivalent in dosage form, route of administration, strength, and indication. Therefore, the only possible dispensing error which could result is that representing a brand switch, which will have no clinical relevance. Therefore, it is the conclusion of this reviewer that the sponsor be permitted to proceed marketing this drug with the name GlucaGen®.

The microbiology section of this application was reviewed under consult by the ONDC Microbiology Staff, HFD-510, and was recomended for approval based on microbiology issues (see microbiologist's review dated 2-23-98).

APPEARS THIS WAY ON ORIGINAL

REMARKS/COMMENTS:
This application provides the CMC information for recombinant Glucagon, which is intended to be prescribed and used exactly as the animal-sourced drug currently on the US market. Glucagon is used to treat severe hypoglycemia and as a diagnostic aid in certain GI tests. This drug represents an advance over the traditional glucagon drug, which was isolated from animal pancreatic glands, in that it has no animal-sourced ingredients, thereby eliminating the potential for BSE transmission, and in that it is highly pure with respect to the original glucagon. (b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4)

(b)(4) The product will be marketed in single-use vials of 1 mg supplied with "sterile water for reconstitution". (b)(4)

(b)(4)

(b)(4) The sponsor has provided adequate evidence of the structure of their drug, and adequate tests and specifications have been implemented to assure the quality of this drug.

APPEARS THIS WAY ON ORIGINAL

CONCLUSIONS & RECOMMENDATIONS:
Several deficiencies exist in the CMC section of the applications. Of primary concern, there is no validation for the removal of (b)(4) s from the drug substance, the limits for the (b)(4) for the drug product have not been properly defined, nor is the assay properly validated, and insufficient drug product stability data have been provided to justify the requested expiry. Inspections are currently underway, or are completed, and the OC recomendation is anticipated to be available prior to the (b)(4). The Microbiology section of the application was reviewed by the Office of New Drug Chemistry Microbiology Staff HFD-805, and recomended for approval with respect to microbiology (see microbiologist's review dated 2-23-98). The labeling and nomenclature committee did not find the approved name "GlucaGen" acceptable, due to its similarity to Glucagon, the USAN name of the produt. However, since this drug is available in only one dosage form and strength from only two (this application representing the second of the two) manufacturers, there is no chance of a despensing error other than brand switch. Therefore, it is the recomendation of this reviewer that the sponsor proceed to market the product with the proprietary name GlucaGen®. This application is approvable (b)(4)

(b)(4)

(b)(4)

cc:
Org. NDA 20-918
HFD-510/Division File
HFD-510/WBerlin/SMoore
HFD-510/CSO/JRhee
HFD-820/JGibbs [#1 only]
R/D Init by: SMoore

/s/

William K. Berlin, Review Chemist

APPEARS THIS WAY ON ORIGINAL

AE
/s/

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