

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-075

CHEMISTRY REVIEW(S)

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

NDA #: 21-075
CHEMISTRY REVIEW #: 3
DATE REVIEWED: 15-DEC-1999

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	25-JUN-1999	28-JUN-1999	06-JUL-1999
AMENDMENT	14-DEC-1999	15-DEC-1999	

NAME & ADDRESS OF APPLICANT:
Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990
650-225-1202

DRUG PRODUCT NAME
Proprietary: Nutropin Depot
Established: somatropin for injectable suspension
Code Name/#: rhGH
Chem.Type/Ther.Class: 1 P

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

PHARMACOLOGICAL CATEGORY/INDICATION: Treatment of growth failure due to a lack of adequate endogenous growth hormone secretion

DOSAGE FORM: Lyophilized microspheres for injection
STRENGTHS: 13 mg/vial, 18 mg/vial and 22.5 mg/vial
ROUTE OF ADMINISTRATION: Sub-cutaneous injection
DISPENSED: Rx OTC
SPECIAL PRODUCTS: Yes No

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

Somatropin; Recombinant human growth hormone; CAS-12629-01-5.

SUPPORTING DOCUMENTS:

See Chemistry Review #1.

RELATED DOCUMENTS:

See Chemistry Review #1.

NDA:

See Chemistry Review #1.

CONSULTS:

N/A

REMARKS:

This Amendment was submitted in response to a request from Biopharm for revised dissolution specifications and were determined to be acceptable (see Biopharm review). Satisfactory.

CONCLUSIONS & RECOMMENDATIONS:

Chemistry, manufacturing and controls (CMC) information remains satisfactory. From this Chemist's point of view, the application can be approved.

cc:
Org. NDA 21-075
HFD-510/Division File
HFD-510/CSO
HFD-510/SMoore

/S/

12-15-99

Stephen K. Moore,
Chemistry Team Leader

R/D Init by:

filename: N21075o.hgh.doc

AP

APPEARS THIS WAY
ON ORIGINAL

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

NDA #: 21-075

CHEMISTRY REVIEW #: 2

DATE REVIEWED: 7-DEC-1999

SUBMISSION TYPE

DOCUMENT DATE

CDER DATE

ASSIGNED DATE

ORIGINAL 25-JUN-1999
AMENDMENT 30-NOV-1999

28-JUN-1999
01-DEC-1999

06-JUL-1999

NAME & ADDRESS OF APPLICANT:

Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990
650-225-1202

DRUG PRODUCT NAME

Proprietary:

Established:

Code Name/#:

Chem.Type/Ther.Class:

Nutropin Depot
somatropin for injectable suspension
rhGH
1 P

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

PHARMACOLOGICAL CATEGORY//INDICATION:

Treatment of growth failure due to a lack of adequate endogenous growth hormone secretion

DOSAGE FORM:

Lyophilized microspheres for injection

STRENGTHS:

13 mg/vial, 18 mg/vial and 22.5 mg/vial

ROUTE OF ADMINISTRATION:

Sub-cutaneous injection

DISPENSED:

Rx OTC

SPECIAL PRODUCTS:

Yes No

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

Somatropin; Recombinant human growth hormone; CAS-12629-01-5.

SUPPORTING DOCUMENTS:

See Chemistry Review #1.

RELATED DOCUMENTS:

See Chemistry Review #1.

NDA:

See Chemistry Review #1.

CONSULTS:

N/A

REMARKS:

This Amendment dated 11-30-99 provides a response to the Information Request for CMC Information sent by FAX to the firm on 11-19-99. A stability update is also provided.

CONCLUSIONS & RECOMMENDATIONS:

Chemistry, manufacturing and controls (CMC) information is satisfactory. From this Chemist's point of view, the application can be approved.

cc:
Org. NDA 21-075
HFD-510/Division File
HFD-510/CSO
HFD-510/SMoore
HFD-102/JJGibbs
R/D Init by:

/S/

12/7/99

Stephen K. Moore,
Chemistry Team Leader

filename: N21075o.hgh.doc

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APPEARS THIS WAY
ON ORIGINAL

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

NDA #: 21-075
CHEMISTRY REVIEW #: 1

DATE REVIEWED: 23-NOV-1999

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	25-JUN-1999	28-JUN-1999	06-JUL-1999
AMENDMENT	22- NOV -1999 OCT	25- NOV -1999 OCT	

NAME & ADDRESS OF APPLICANT:

Genentech, Inc.
1 DNA Way
South San Francisco, CA 94080-4990
650-225-1202

DRUG PRODUCT NAME

Proprietary:
Established:
Code Name#:
Chem. Type/Ther. Class:

Nutropin Depot
somatropin for injectable suspension
rhGH
1 P

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

PHARMACOLOGICAL CATEGORY/INDICATION:

Treatment of growth failure due to a lack of adequate endogenous growth hormone secretion

DOSAGE FORM:

Lyophilized microspheres for injection

STRENGTHS:

13 mg/vial, 18 mg/vial and 22.5 mg/vial

ROUTE OF ADMINISTRATION:

Sub-cutaneous injection

DISPENSED:

Rx OTC

SPECIAL PRODUCTS:

Yes No

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

Somatropin; Recombinant human growth hormone; CAS-12629-01-5. For structure, see attached.

SUPPORTING DOCUMENTS:

See p. 1 of Chemistry Review Notes

RELATED DOCUMENTS:

[redacted] rhGH; [redacted] Genentech.

NDA:

N 19-107, Protropin, Genentech

N 19-676, 20-168 and 20-656, Nutropin, Genentech

N 20-522, Nutropin AQ, Genentech

CONSULTS:

Microbiology

REMARKS:

Nutropin Depot is the first formulation of somatropin as an injectable suspension. The depot formulation is designed for either once or twice-monthly injections. The formulation consists of recombinant human growth hormone (rhGH) embedded in microspheres. The microspheres are comprised of a biodegradable matrix of poly D/L lactide-co-glycolide. The free-flowing powder is suspended in a designated diluent to produce a slurry that is administered immediately by subcutaneous injection. Following injection, rhGH is released from the microspheres, initially by diffusion, followed by polymer degradation and diffusion.

Three strengths of Nutropin Depot are described, 13 mg/vial, 18 mg/vial and 22.5 mg/vial. Since the suspension is viscous and prevents complete withdrawal of the entire vial contents, the vials are overfilled to ensure delivery of the labeled amount of somatropin. Each strength is supplied in a kit containing a vial of Nutropin Depot, a vial of diluent, a syringe and three needles.

rhGH microspheres are manufactured by [redacted] (Briefly)

The active ingredient of Nutropin Depot, somatropin, is produced by fermentation in *E. coli* by [redacted]. The amino acid sequence is identical to that of human pituitary-derived growth hormone. The drug substance is liquid rhGH Bulk Solution in [redacted] Buffer.

The Amendment dated 10-22-99 provides revised diluent vial labeling, updated stability information for rhGH Zinc-Acetate Powder and revised expiration date, and a formal copy of the FAX communications sent to FDA.

This NDA was originally assigned to William Berlin, Ph.D.. Dr. Berlin initiated the primary NDA review, however, he was unable to complete the review before leaving the Agency. Dr. Berlin completed the primary review of DMF [redacted] for [redacted] containers. Chien-Hua Niu, Ph.D. performed the primary review of DMF [redacted] for Poly (D,L-lactide-co-glycolide). Completion of the review of this NDA as well as the review of DMF [redacted] for [redacted] Diluent were performed by this reviewer.

CONCLUSIONS & RECOMMENDATIONS:

Chemistry, manufacturing and controls (CMC) information is not satisfactory. From this Chemist's point of view, the application is approvable, provided the applicant addresses the deficiencies and comments (see Draft Letter). The Establishment Evaluation Request (EER) is pending.

cc:
Org. NDA 21-075
HFD-510/Division File
HFD-510/CSO
HFD-510/SMoore
HFD-102/JJGibbs
R/D Init by:

[redacted] /S/

Stephen K. Moore,
Chemistry Team Leader

11/23/99

filename: N21075o.hgh.doc

AE

APPEARS THIS WAY
ON ORIGINAL