CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number: 020522/S004

Trade Name: NUTROPIN AQ INJECTION

Generic Name: SOMATROPIN (rDNA ORIGIN)

Sponsor: GENETECH, INC

Approval Date: 12/17/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 020522/S004

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tenative Approval Letter				X
Approvable Letter				X
Final Printed Labeling		X		
Medical Review(s)	X			
Chemistry Review(s)	X			
EA/FONSI	X			
Pharmacology Review(s)				X
Statistical Review(s)				X
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)	X			
Bioequivalence Review(s)				X
Administrative Document(s)/ Correspondence	X			

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 020522/S004

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-522/S-004

DEC 17 1997

Genentech Inc.
Attention: David MacFarlane, Ph.D.
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. MacFarlane:

Please refer to your supplemental new drug application dated August 14, 1997, received August 20, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nutropin AQ™ [somatropin (rDNA origin) injection], 10 mg/vial.

We acknowledge receipt of your submissions dated September 5, and December 15, 1997 . The User Fee goal date for this application is August 20, 1998.

This supplemental new drug application provides for the new indication for the replacement of endogenous growth hormone in adult patients with growth hormone deficiency.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submission dated December 15, 1997. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on December 15, 1997. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-522/S-004. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-

up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Should a letter communicating important information about this drug product (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to these NDAs and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Michael F. Johnston, R.Ph., Project Manager, at (301) 827-6423.

Sincerely yours,

/S/ 12/17/97

APPEARS THIS WAY
ON ORIGINAL

Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc: Original NDA 20-522
HFD-510/Div. files
HFD-510/CSO/MJohnston/SMalozowski/GFleming/DHertig/RSteigerwalt/
WBerlin/SMoorE/EGalliers/SSobel
HFD-870/RShore/HAhn
HFD-002/ORM (with labeling)
HFD-102/Office Director
HFD-101/L.Carter
HFD-820/ONDC Division Director
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling) - for all NDAs and supplements for adverse reaction changes.
HFI-20/Press Office (with labeling)
HFD-021/ACS (with labeling)

Drafted by: Mjohnston12.xx.97/ File: wpfiles\n20522\S04ap
Initialed by: SEE CLEARANCE CHART
final: MJohnston12.15.97

APPROVAL (AP)

FINAL PRINTED LABELING HAS NOT BEEN SUBMITTED TO THE FDA.

DRAFT LABELING IS NO LONGER BEING SUPPLIED SO AS TO ENSURE ONLY CORRECT AND CURRENT INFORMATION IS DISSEMINATED TO THE PUBLIC.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020522/S004

MEDICAL REVIEW(S)

DEC 5 1997

NDA 20-522
Nutropin AQ
rhGH

Genentech, Inc.
Received 8/14/97
Forwarded 9/3/97
Reviewed 12/2/97

MEDICAL OFFICER'S REVIEW OF A NDA SUPPLEMENT (SE1-004)

The sponsor is submitting information to support the approval of the use of Nutropin AQ in growth hormone deficient adults. This product has been shown to be bioequivalent with the already approved product Nutropin (11/8/95 NDA 20552). The only difference between these products is their formulation. While Nutropin is lyophilized, Nutropin AQ is liquid. No medical information is enclosed with this document. Therefore, as previously done with the Turner's indication, this NDA could be approved based in the biopharmacological review alone because these two products are bioequivalent. The recommendations of the biopharmacological reviewer should be submitted to the sponsor to be incorporated in the label. In addition, I have requested the sponsor to submit all available information on the use of Nutropin AQ in adults to assess whether the local reactions at the injection site differ form those described in pediatric patients. In the meantime, I recommend to follow the advice of the Biopharmaceutic Division to approve this NDA.

/S/

APPEARS THIS WAY
ON ORIGINAL

Saul Malozowski, M.D., Ph.D.

cc: NDA Arch.
HFD-510-file
HFD-510/AFleming/MJohnston/SMalozowski/12/2/97

Concur that no clinical issues are involved. The NDA can be approved based on showing bioequivalence to the reference drug product.

/S/

APPEARS THIS WAY
ON ORIGINAL

12/5/97

NDA 20-522/S-004
Nutropin AQ
rhGH

Genentech, Inc.

MEDICAL OFFICER'S REVIEW OF SAFETY OF A NDA SUPPLEMENT S-004

The safety profile of this drug is not different from that reported in the original NDA. The label adequately reflects its' safety profile. We are in the process, however, of analyzing whether local injection site reactions are more common with this formulation. No formal responses have yet been received. The sponsor is committed to make the necessary changes in the label if findings of local reactions with this formulation is different form those observed with other formulations.

/S/

Saul Malozowski, M.D., Ph.D.

cc: NDA Arch.
HFD-510-file
HFD-510/AFleming/MJohnston/SMalozowski/12/2/97

/S/
12/5/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020522/S004

CHEMISTRY REVIEW(S)

CHEMISTS REVIEW	1. ORGANIZATION	2. NDA NUMBER OCT 27 1997
	DMEDP II, HFD-510	20-522
3. NAME AND ADDRESS OF APPLICANT		4. SUPPLEMENT NUMBER, DATE
Genentech, Inc. Point San Bruno Boulevard MS48 San Francisco, CA 94080-4990		SE1-004 12-13-97
5. PROPRIETARY NAME	6. NAME OF THE DRUG	7. AMENDMENTS, REPORT, DATE
Nutropin AQ	somatropin (rDNA origin) for injection	

8. SUPPLEMENT PROVIDES FOR

A new indication for replacement therapy in growth hormone-deficient adults.

9. PHARMACOLOGICAL CATEGORY	10. HOW DISPENSED	11. RELATED IND, NDA, DMF
growth hormone	RX	
12. DOSAGE FORM	13. POTENCY	
injection	10 mg/vial	

14. CHEMICAL NAME AND STRUCTURE

See Chemistry Review #1

15. COMMENTS

The supplement provides for a new indication to treat growth hormone-deficient adults. Clinical data for this application is being referenced from N 19-676, SE1-009. The Indications and Usage and Dose and Administration sections were updated to provide for this indication, as well as editorial corrections (mainly to comply with Pediatric patient labeling requirements). Also, the application contains a claim of categorical exclusion under 21 CFR 25.31(c), and the sponsor stated that the indication will not cause an increase in distribution of the drug and that no special circumstances exist. The request for a waiver of the EA requirement is acceptable.

16. CONCLUSION AND RECOMMENDATION

The sponsor has provided adequate labeling, from a chemistry standpoint, and has provided an acceptable request to waive the requirements to submit an updated EA. This application may be approved based on chemistry issues.

17. NAME	18. REVIEWERS SIGNATURE	19. DATE COMPLETED
WILLIAM K. BERLIN	/S/	10-15-97

DISTRIBUTION: ORIGINAL JACKET CSO REVIEWER DIVISION FILE

/S/
10/27/97

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020522/S004

ENVIRONMENTAL ASSESSMENT AND/OR FONSI

NDA SUPPLEMENT: ITEM 4

NAME OF DRUG: Nutropin AQ™ [somatropin (rDNA origin) injection]—Adult Growth Hormone Deficiency

4.D ENVIRONMENTAL ASSESSMENT

Genentech, Inc. claims a categorical exclusion to the environmental assessment requirements in accordance with 21 CFR Part 25.31(c), since this action will not alter significantly the concentration or distribution of growth hormone, its metabolites, or degradation products in the environment. To our knowledge, no extraordinary circumstances exist.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020522/S004

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA: 20-522/SE1-004	**SUBMISSION DATE:**	**08/14/97**
BRAND NAME:	**Nutropin AQ™**	
GENERIC NAME:	**somatropin (rDNA origin) injection**	
REVIEWER:	**Robert M. Shore, Pharm.D.**	
SPONSOR:	**Genentech, Inc., S. San Francisco, CA**	
TYPE OF SUBMISSION:	**Efficacy Supplement**	

NOV 14 1997

SYNOPSIS:

Currently, Nutropin AQ™ (liquid formulation) is approved for treatment of growth failure in children with growth hormone deficiency (GHD), chronic renal insufficiency, and Turners Syndrome. This submission seeks approval of Nutropin AQ™ for use in Adult GHD.

Nutropin® lyophilized powder is currently under review for use in Adult GHD (NDA 19-676/SE1-009). Nutropin AQ™ liquid formulation has been accepted as bioequivalent to Nutropin™ lyophilized formulation (see OCPB review dated 11/08/95 for NDA 20-522). Genentech has submitted draft labeling for Nutropin AQ™ which is consistent with the currently approved labeling for Nutropin™.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II (OCPB/DPE-2) has reviewed NDA 20-522/SE1-004 submitted 08/14/97. No final determination can be made at this time as to the acceptability of Nutropin AQ™ for the Adult GHD indication because Nutropin is still under review for this indication. If Nutropin is approved for use in Adult GHD, then Nutropin AQ™ would be acceptable for the same indication since the two products are bioequivalent. Labeling recommendations for Nutropin AQ™ are the same as for Nutropin® and are included below for completeness. Recommendation and labeling comments should be sent to the sponsor.

LABELING COMMENTS:

(~~Strikeout text~~ should be removed from labeling; **Redline text** should be added to labeling; Boxed text is for explanation only and is not intended to be included in the labeling)

Pharmacokinetics

Subcutaneous Absorption-The absolute bioavailability of recombinant human growth hormone (rhGH) after subcutaneous administration in healthy adult males has been determined to be 81%±20%...

Special Populations

Gender-...Available data for methionyl recombinant growth hormone, pituitary-derived growth hormone, and endogenous suggest...

Geriatrics-Limited published data suggest that the plasma clearance and average steady-state plasma

concentration of rhGH may not be different between young and elderly males.

Sohmiya et al., 1992 (Reference number 27, Volume 4 of 40)

APPEARS THIS WAY
ON ORIGINAL

Robert M. Shore, Pharm.D. /S/ 11/14/97
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

RD/FT initialed by Hae-Young Ahn, Ph.D., Team Leader_ /S/ 11/14/97

CC: NDA 20-522/SE1-004 (orig.,1 copy), HFD-510(Malozowski, Johnston), HFD-870(Ahn, Shore, M. Chen), HFD-340(Vishwanathan), CDR (Murphy)

code: AE

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020522/S004

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

NEW DRUG APPLICATION: ITEM 14

NAME OF DRUG: **Nutropin® Liquid [somatropin (rDNA origin) injection]– Growth Hormone Deficiency**

14. PATENT CERTIFICATION WITH RESPECT TO ANY PATENT WHICH CLAIMS THE DRUG

21 U.S.C. 355(b)(2): An application for a drug for which investigations relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted shall also include a certification. . .

(i) that such patent information has not been filed;

(ii) that such patent has expired;

(iii) the date on which such patent will expire; or

(iv) that such patent is invalid or will not be infringed by the manufacture, use or sale of the new drug for which the application is submitted.

All investigations in this application were conducted by or for the applicant; hence, this section is not applicable.

APPEARS THIS WAY
ON ORIGINAL

NDA SUPPLEMENT: ITEM 13

NAME OF DRUG: Nutropin AQ™ [somatropin (rDNA origin) injection]—Turner Syndrome

13. PATENT INFORMATION ON ANY PATENT WHICH CLAIMS THE DRUG

21 U.S.C. 355(b): The applicant shall file with the application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use or sale of the drug.

The patent covering Nutropin® Liquid [somatropin (rDNA origin) injection] is being prosecuted under International Patent Application No. PCT/US93/07149 filed on July 29, 1993. This application, now nationalized in the U.S., has been assigned application number 08/117,156 and is a continuation–in–part of U.S. patent application 07/923,401, now abandoned.

All subsequent pages of Item 13 remain the same.

APPEARS THIS WAY
ON ORIGINAL

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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 ON PAGE 8 (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.

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, 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.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #_____ _____
NDA #_____ _____
NDA # _____ _____

2. Combination product.

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 any one 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).

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 6. 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 /___/ NO /_X_/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 6.

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 /___/ NO /___/

   If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

   _____

   _____

   (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 /___/ NO /___/

(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 /___/ NO /___/

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 /___/ NO /___/

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 # _____

Investigation #2, 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 /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

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 /___/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

c) 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_, Study # _____

Investigation #2_, Study # _____

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

IND # _____ YES /___/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ NO /___/ 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 /___/ Explain _____ NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ NO /___/ 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 /___/

If yes, explain: _____

_____

/S/

Michael F. Johnston
Signature of Project Manager

9-15-97
Date

/S/

Solomon Sobel M.D.
Signature of Division Director

12-17-97
Date

APPEARS THIS WAY
ON ORIGINAL

cc: Original NDA
Division File
HFD-85 Mary Ann Holovac (original)

APPEARS THIS WAY
ON ORIGINAL

CERTIFICATION STATEMENT
[Section 306(k)(1) of the Act (21 U.S.C. 335a(k)(1)]

This is to certify that Genentech, Inc. has not and will not use, in any capacity, the services of any person debarred under subsections (a) or (b) [Section 306(a) or (b)], in connection with this New Drug Application (NDA).

Signed by: _____

M. David MacFarlane, Ph.D.

Title: Vice President, Regulatory Affairs

Date: 12/13/96

APPEARS THIS WAY
ON ORIGINAL

Genentech, Inc.

DEPARTMENT OF REGULATORY AFFAIRS

460 Point San Bruno Boulevard MS48
South San Francisco, CA 94080-4990
(415) 225-1558
FAX (415) 225-1397

September 5, 1997

Dr. Solomon Sobel, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Food and Drug Administration
Center for Drug Evaluation and Research (HFD-510)
Attention: Document Control Room, 14-B-19
5600 Fishers Lane
Rockville, Maryland 20857

SEP 10 1997
HFD-510

Subject: NDA 20-522, S-008
Nutropin AQ® [(somatropin (rDNA origin) injection]
Response to FDA Request for Information

Dear Dr. Sobel:

Reference is made to our labeling supplement to NDA 20-522, S-008, submitted August 14, 1997 for use of Nutropin AQ® as replacement therapy in growth hormone-deficient adults. In response to a request from Michael Johnston, CSO, this submission provides a copy of the patent information and debarment statement information relevant to the August 14, 1997 supplement. Please note that no clinical studies in adult GHD patients were performed using Nutropin AQ®, as NDA 20-522, S-008 is based on bioequivalence to the lyophilized Nutropin product and cross-referenced to NDA 19-676, S-009. As such, a copy of the debarment statement from NDA 19-676, S-009 is included in this submission.

If you have any comments or questions regarding this submission, please contact Ms. Christie Zustak of my staff at (650) 225-2038.

Sincerely,

M. David MacFarlane, Ph.D.
Vice President
Regulatory Affairs

20522-051 sub mo'c

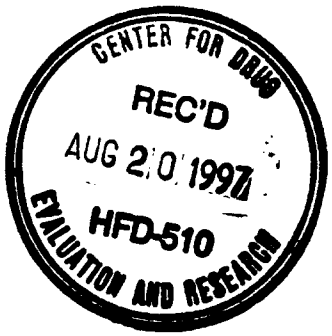
Genentech, Inc.

DEPARTMENT OF REGULATORY AFFAIRS

460 Point San Bruno Boulevard MS48
South San Francisco, CA 94080-4990
(415) 225-1558
FAX: (415) 225-1397

August 14, 1997

Solomon Sobel, M.D.
Director
Division of Metabolic and
Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
Attn: Document Control Room, 14B-03
5600 Fishers Lane
Rockville, MD 20857



Subject: NDA 20-522
Nutropin AQ™ [somatropin (rDNA origin) injection]
Revisions to Package Insert - Additional Label Claim

Dear Dr. Sobel:

Reference is made to our New Drug Application, NDA 20-522, for Nutropin AQ™ [somatropin (rDNA origin) injection], initially approved on December 29, 1995. As is reflected in the currently approved labeling, Nutropin AQ has been determined to be bioequivalent to lyophilized Nutropin, based on the statistical evaluation of AUC and C_{max}.

Based on established bioequivalence to lyophilized Nutropin, this submission adds an additional indication to the Nutropin AQ™ labeling; that is, replacement of endogenous GH in patients with adult GH deficiency (GHD) syndrome. Currently this indication is under review for lyophilized Nutropin (reference NDA 19-676, S-009, submitted December 13, 1996). Genentech, Inc. is submitting the revised labeling for Nutropin AQ at this time to make possible a simultaneous review of the Adult GHD indication labeling for both Nutropin and Nutropin AQ.

20522-049 sub ss

Enclosed is a revised package insert for Nutropin AQ™ [somatropin (rDNA origin) injection] with the Adult GHD indication added. The new changes are indicated by underline (additions) or strike-through (deletions).

Additionally, instead of submitting an Environmental Assessment with this NDA supplement, Genentech, Inc. claims a categorical exclusion, per 21 CFR 25.31. Included is an attachment citing the particular categorical exclusion that is claimed along with a statement that, to Genentech, Inc.'s knowledge, no extraordinary circumstances exist.

Should you have any questions regarding this submission please contact Ms. Christie Zustak of my staff at (650) 225-2038.

Sincerely,

M. David MacFarlane, Ph.D.
Vice President
Regulatory Affairs

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-522/S-004

AUG 28 1997

GENENTECH, INC.
460 Point San Bruno Boulevard
South San Francisco, California 94080-4990

Attention: M. David MacFarlane , Ph. D., Vice-President, Regulatory Affairs

Dear Dr. MacFarlane:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: NUTROPIN AQ (somatropin (rDNA origin) Injection

NDA Number: 20-522

Supplement Number: S-004

Date of Supplement: August 14, 1997

Date of Receipt: August 20, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on October 19, 1997, in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Attention: Document Control Room 14B-19
5600 Fishers Lane
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Sincerely.

/S/

Enid Galliers
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cc:
Original NDA 20-522/S-004
HFD-510/Div. Files
HFD-510/CSO/M. Johnston

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SUPPLEMENT ACKNOWLEDGEMENT