CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE for:

APPLICATION NUMBER: 020522/S002

TRADE NAME: Nutropin AQ 10 mg/vial

GENERIC NAME: Somatropin (rDNA origin) injection

SPONSOR: Genentech, Inc.

APPROVAL DATE: 03/24/97

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-522/S-002

MAR 24 1997

Genentech Inc.
Attention: David MacFarlane, Ph.D.
460 Point San Bruno Boulevard
South San Francisco, CA 94080-4990

Dear Dr. MacFarlane:

Please refer to your supplemental new drug application dated January 21, 1997, received January 22, 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 submission dated March 14, 1997. The User Fee goal date for this application is January 22, 1998.

This supplemental new drug application provides for the new indication of the treatment of growth failure associated with Turner Syndrome.

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 March 14, 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 March 14, 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-002. 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., Consumer Safety Officer, at (301) 443-3490.

Sincerely yours,

Solomon Sobel

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

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.

Please reference Volume 1, pages 4–32 of the original NDA submission, submitted November 9, 1994. The wording on page 4 of that submission has been updated as follows:

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.

EXCLUSIVITY SUMMARY for NDA # 20-522 SUPPL # 002

Trade Name Nutropin AQ Generic Name [somatropin (rDNA origin) liquid injection]
Applicant Name Genentec, Inc. HFD- 510 Approval Date

PART I. IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES /__/ NO /_X_/

   b) Is it an effectiveness supplement? YES /_X_/ NO /___/

   If yes, what type? (SE1, SE2, etc.) SE1

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /__/ NO /_X_/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   This supplement is based solely on bioequivalence with the Nutropin product

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   ---

   d) Did the applicant request exclusivity? YES /___/ NO /_X_/

   If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCK ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /_X_/

If yes, NDA #_____ Drug Name_____

NDA #_____ Drug Name_____

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 /_X_/ NO /___/

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

NDA # 20-522 ___ Nutropin AQ ___

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 8. 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 8.

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: _____

_____

Michael F. Johnston
Signature of Project Manager

3-13-97
Date

Solomon Sobel M.D.
Signature of Division Director

3/23/97
Date

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

NDA 20-522/SE1-002

Nutropin AQ: Turners Syndrome

This is not a new molecular entity therefore, pediatric page is not required for this NDA

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 NDA.

Signed by: _____
M. David MacFarlane, Ph.D.

Title: Vice President, Regulatory Affairs

Date: Jan 21, 1997

NDA 20-6522/SE1-002

Nutropin AQ: Turners Syndrome

No Division of Scientific Investigations Reviews were Requested for this NDA

NDA 20-522
Nutropin AQ
rhGH

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

MEDICAL OFFICER'S REVIEW OF AN NDA SUPPLEMENT

The sponsor is submitting information to support the approval of the use of Nutropin AQ in girls with Turners syndrome. This product has been shown to be bioequivalent with the already approved product Nutropin. 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 and I believe that it could be approved based in the biopharmacological review.
Therefore, I recommend to follow the recommendation of the Biopharm Division on whether to approve or not this NDA.

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

Concur,
A Fleming
3/12/97

cc: NDA Arch.
HFD-510-file
HFD-510/AFleming/MJohnston/SMalozowski/3/12/97

NDA 20-522/SE1-002

Nutropin AQ: Turners Syndrome

Due to the approval being based on bioequivalence alone, no statistical review were conducted on this NDA supplement.

Clinical Pharmacology & Biopharmaceutics Review

NDA: 20-522	**SUBMISSION DATE:**	**January 21, 1997**
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 (revisions to package insert)**	

SYNOPSIS:

This submission, dated January 21, 1997, is for Nutropin AQ™ [somatropin (rDNA origin) injection]. Currently, Nutropin AQ™ (liquid formulation) is used for treatment of growth failure in children with growth hormone deficiency and chronic renal insufficiency, as per approved NDA 20-522. Nutropin™ (lyophilized powder) is approved for these two indications, as well as for growth failure associated with Turners Syndrome, as per approved NDA 20-656. This submission seeks to add the Turner's Syndrome indication to Nutropin AQ™.

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 has reviewed NDA 20-522 (revisions to package insert) submitted 01/21/97 and finds it acceptable.

Robert M. Shore, Pharm.D. Robert M Shore 03/12/97
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

FT initialed by Hae-Young Ahn, Ph.D., Team Leader 3/12/97

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

"CH"

NDA 20-522/SE1-002
Nutropin AQ: Turners Syndrome

No new pharmacology information was submitted for this NDA therefore no pharmacology review was conducted.

NDA 20-522/SE1-002

Nutropin AQ: Turners Syndrome

No new chemistry information was submitted for this NDA therefore no chemistry review was conducted.

NDA 20-522/SE1-002

Nutropin AQ: Turners Syndrome

No Establishment Evaluation Requests were requested for this supplement.

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: March 14, 1997

FROM: Michael F. Johnston, Project Manager

SUBJECT: ENVIRONMENTAL ASSESSMENT

TO: File for NDA 20-522/S002

This memo replaces the EA/FONSI for NDA 20-522/S002.

An EA/FONSI is not required for this NDA efficacy supplement. This was agreed upon on March 11, 1997, in a telephone conversation between Stephen Moore and Nancy Sager, Environmental Scientists Team Leader. The potential increase in Nutropin AQ (liquid) usage will be offset by the decrease in Nutropin (lyphilized powder) usage. All other factors (patient numbers, dosages, etc.) remain the same and there is no anticipated environmental harm.

Stephen K. Moore 3-14-97
Stephen Moore, Ph.D.
Chemistry Team Leader I
DNDC II @ HFD-510

3/14/97
Michael F. Johnston, R.Ph.
Project Manager, DMEDP
HFD-510

cc: NDA 20-522
HFD-510 /Division Files
HFD-510/WBerlin/SMoore/MJohnston

NDA 20-522/SE1-002

Nutropin AQ: Turners Syndrome

No new microbiology information was submitted for this NDA therefore no microbiology review was conducted.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

Date FEB 12 1997

NDA No. 20-522

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

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

Dear Sir/Madam:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: NUTROPIN AQ

NDA Number: 20-522

Supplement Number: S-002

Date of Supplement: January 21, 1997

Date of Receipt: January 22, 1997

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on MAR 23 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
Attention: Document Control Room
5600 Fishers Lane, HFD-510
Rockville, MD 20857

Sincerely yours,

Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office Drug Evaluation II
Center for Drug Evaluation and Research

enentech, Inc.

DEPARTMENT OF REGULATORY AFFAIRS

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

March 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, S-002
Nutropin AQ™ [somatropin (rDNA origin) injection]
Re: Package Insert

Dear Dr. Sobel:

Reference is made to our supplemental New Drug Application, 20-522, S-002, for Nutropin® [somatropin (rDNA origin) injection] for treatment of short stature associated with Turner syndrome.

Enclosed is a clean version of the package insert with strike-throughs and underlines eliminated. Additionally, per your Division's request, the following sentence has been added to the Adverse Reactions section:

"Injection site discomfort has been reported. This is more commonly observed in children switched from another growth hormone product to Nutropin AQ."

If we may provide any additional information or if you have any questions regarding this submission, please contact Ms. Christie Zustak of my staff at (415) 225-2038.

Sincerely,

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

20522-038 sub ss

NDA 20-522/SE1-002

Nutropin AQ: Turners Syndrome

There were no meeting minutes associated with this supplemental application.

NDA 20-522/SE1-002

Nutropin AQ: Turners Syndrome

There was no Advisory Committee Meeting conducted for this supplemental NDA.

NDA 20-522/SE1-002

Nutropin AQ: Turners Syndrome

Advertising Materials have not been supplied but are requested on the Approval Letter