CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-522/S-013

CORRESPONDENCE

Genentech, Inc.
Genentech, Inc.
Genentech, Inc.
Genentech, Inc.
Genentech, Inc.

1 DNA Way
South San Francisco, CA 94080-4990
(650) 225-1000

To: Enid Galliers	To:
Fax: 301 443 9282	Fax:
Company: FDA	Company:
Dept: DMEDP	Dept:

From: Fiona Cameron, Regulatory Affairs
Tel: (650) 225-1818
Fax: (650) 225-1397

Date: 4/6/00

Number of Pages: 2 (including this one)

Reference: Nutropin NDA 19-676, S-016 Pubertal Dosing Supplement

Dear Enid:

As you requested, attached is our Environmental Assessment for the Nutropin pubertal dosing submission. We are requesting a categorical exclusion.

Please let me know if you have any questions, and thanks for your help with this.

Best regards

Fiona

Fiona Cameron
cameron2@gene.com

NDA LABELING SUPPLEMENT (PUBERTAL DOSING): ITEM 4
Nutropin® [somatropin (rDNA origin) for injection]

4. CHEMISTRY, MAUNFACTURING AND CONTROLS

4.A.5 Environmental Assessment

DATE OF SUBMISSION

6 April 2000

NAME AND ADDRESS OF APPLICANT/PETITIONER

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

DESCRIPTION OF PROPOSED ACTION

As specified in regulation at 21 CFR Section 25.15(d), Genentech, Inc. states that this NDA supplement for the pubertal dosing regimen of Nutropin qualifies for a categorical exclusion from the Environmental Assessment (EA) requirement. Specifically, under 21 CFR Section 25.31(b), any action on an NDA, abbreviated application, application for marketing approval of a biologic product or a supplement to these applications is categorically excluded and ordinarily does not require the preparation of an EA or an Environmental Impact Statement if the action increases the use of the active moiety, but the estimated concentration of the substance at the point of entry into the aquatic environment will be below 1 part per billion.

Using the formula and guidelines provided in Section III.A.2. of the Guidance for Industry – Environmental Assessment of Human Drug and Biologics Applications (Revision 1, July 1998), Genentech has determined that the estimated concentration of the substance at the point of entry into the aquatic environment from use will be below 1 part per billion. To Genentech's knowledge, no extraordinary circumstances exist.

JUL - 7 1999

NDA 20-522/S-013

Genentech, Inc.
Attention: Robert L. Garnick, Ph.D.
Vice President, Regulatory Affairs
1 DNA Way
South San Francisco, CA 94080-4990

Dear Dr. Garnick:

We acknowledge receipt of your efficacy supplemental application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Nutropin AQ (somatropin [rDNA origin] injection)
NDA Number:	20-522
Supplement Number:	S-013
Therapeutic Classification:	Standard (S)
Date of Supplement:	June 24, 1999
Date of Receipt:	June 28, 1999

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on August 27, 1999, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be April 28, 2000, and the secondary user fee goal date will be June 28, 2000.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 314.55.

If you believe that this drug qualifies for a waiver of the study of the pediatric study requirement,

you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov.cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. If you do not submit a Proposed Pediatric Study Request within 120 days from the date of this letter, we will presume that you are not interested in obtaining pediatric exclusivity and will notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity.

Please cite the application number listed above at the top of the first page of any communications concerning this application. All communications concerning this supplemental application should be addressed as follows:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room 14B-19
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, contact Crystal King, P.D., M.G.A., Regulatory Project Manager, at (301) 827-6423.

Sincerely,

/ /

ES

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

cc:
Archival NDA 20-522/S-013
HFD-510/Div. Files
HFD-510/C.King
HFD-510/Reviewers and Team Leaders
DISTRICT OFFICE

Drafted by: CKing/07.05.99
Initialed by: EGalliers/07.06.99
final: CKing/07.06.99
filename: mydoc/NDA/20522/20522/s013/ack070599

SUPPLEMENT ACKNOWLEDGEMENT (AC)

Cross-reference:
NDA 19-676, S-016

Genentech, Inc.

1 DNA Way
South San Francisco, CA 94080-4990
(650) 225-1000
FAX (650) 225-6000

April 11, 2000

John Jenkins, M.D.
Acting Director
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Subject: **NDA 20-522**, S-013
Nutropin AQ® Pubertal Dosing Supplement
Amendment to a Pending Application
Item 2 – Labeling
Item 4 – Chemistry, Manufacturing and Controls
Environmental Assessment

Dear Dr. Jenkins:

Reference is made to our Supplemental New Drug Application, NDA 20-522, S-013 for Nutropin AQ® [somatropin (rDNA origin) for injection], submitted on June 24, 1999 for the addition of a higher pubertal dose for pubertal patients being treated for growth failure due to a lack of adequate endogenous growth hormone secretion. Reference is also made to submissions dated August 11, 1999 for a waiver of the requirement to conduct pediatric studies, and March 21, 2000 containing patent information.

A supplement providing clinical data to support the addition of the higher pubertal dose was submitted to Nutropin® NDA 19-676 (S-016, dated June 11, 1999), and was updated with a safety update submitted on November 19, 1999, responses to questions submitted March 27, 2000, draft labeling submitted on March 30, 2000 and final draft labeling submitted on April 10, 2000. These Nutropin submissions are therefore cross-referenced and

the data contained therein is considered to be applicable to Nutropin AQ, based on the established bioequivalence of the two products.

This submission comprises the final version of both the redlined and clean package insert for Nutropin AQ showing the new pubertal dosing text, consistent with that filed to NDA 19-676 on April 11, 2000, and an Environmental Assessment. A complete desk copy of all the items is provided in a black binder for Ms. Crystal King, P.D., M.G.A., Project Manager. The archival copy is contained in the blue binder, and the review copies are contained in the appropriate colored binders.

In addition, as a Phase IV commitment and consistent with that agreed to for Nutropin NDA 19-676, Genentech agrees to provide the following updates for the four-year period following the commercial launch of the pubertal dose regimen:

- NDA Annual Reports (Nutropin and Nutropin AQ)
  We will create a subsection of the NCGS update section and use this to report the number of patients receiving a dose greater than or equal to 0.4 mg/kg and discuss any other information available relevant to these patients.
- Periodic Safety Reports (Nutropin and Nutropin AQ)
  We will create a section that describes the spontaneous adverse event reports and the safety information from NCGS for patients receiving greater than or equal to 0.4 mg/kg dosing, and discusses the safety profile of these patients, as compared to patients receiving doses of less than 0.4 mg/kg (excluding Turner Syndrome and Chronic Renal Insufficiency patients).
- Expedited Adverse Event Reports (Nutropin and Nutropin AQ)
  For any relevant expedited adverse events reports, at the beginning of the narrative in section B-5, "Describe Event or Problem," of the MedWatch Form 3500A, we will use surrounding asterisks to emphasize that the patient was being dosed at greater than or equal to 0.4 mg/kg/week. We will also include this information in the cover letter that accompanies each of these reports, again highlighted in such a manner as to draw immediate attention to the fact.

Please contact Ms. Fiona Cameron, Senior Manager, at (650) 225-1818, by fax at (650) 225-1397, or by email at cameron.fiona@gene.com if you have any other questions regarding the content of the application. We look forward to working with you during your review of this information.

Sincerely,

Robert L. Garnick, Ph.D.
Vice President
Regulatory Affairs

20522-101 sub ss

Genentech, Inc.

NDA SUPP AMEND
SE2-013-SNC

ORIGINAL

1 DNA Way
South San Francisco, CA 94080-4990
(650) 225-1000
FAX: (650) 225-6000

March 21, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAR 2 2 2000
HFD-510

John Jenkins, M.D.
Acting 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-013**
Nutropin AQ® [somatropin (rDNA origin) injection]
Pubertal Dosing Supplement – Items 13 and 14

Dear Dr. Jenkins:

In response to Ms. Crystal King's request of March 19, 2000, please find attached Item 13, Patent Information on Any Patent Which Claims the Drug, and Item 14, Patent Certification with Respect to Any Patent Which Claims the Drug, for NDA 20-522, S-013 for Pubertal Dosing.

Should you have any questions regarding this submission please contact Lawrence W. Davenport, Ph.D., of my staff at (650) 225-1699.

Sincerely,

Robert L. Garnick, Ph.D.
Vice President
Regulatory Affairs

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO
CSO INITIALS DATE

20522-100 sub ss

ORIGINAL

SUPPL NEW CORRESP
5E2-013-SNC

Genentech, Inc.

1 DNA Way
South San Francisco, CA 94080-4990
(650) 225-1000
FAX: (650) 225-6000

August 11, 1999

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-013**
Nutropin AQ® [somatropin (rDNA origin) injection]
Labeling Supplement – Pubertal Dosing
Request for Waiver of Requirement to Conduct Pediatric Studies
[21CFR 201.23(a)]

Dear Dr. Sobel:

Reference is made to our Supplemental New Drug Application, NDA 20-522, S-013, for Nutropin AQ® [somatropin (rDNA origin) injection], submitted on June 24, 1999 for the addition of a higher pubertal dose for pubertal patients being treated for growth failure due to a lack of adequate endogenous growth hormone secretion.

Further to a telephone conversation with Crystal King of your office, and in regard to the FDA Final Rule: Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, we are requesting a waiver from the requirements of 21CFR 201.23(a), under subpart (c)(1), on the basis that adequate pediatric studies have already been performed with Nutropin AQ and Nutropin® [somatropin (rDNA origin) for injection].

20522-096 sub ss

The studies already performed in pediatrics include:

- Study L0368g in NDA 20-522, and studies 86-061 and 87-070 in NDA 19-676, for pediatric growth hormone deficiency.
- Studies 87-069 and M0079g in NDA 20-168, for growth failure associated with chronic renal insufficiency.
- Study 85-044 in NDA 20-656, for short stature associated with Turner syndrome.
- Study M0380g in IND 27,603, for pubertal dosing in pediatric growth hormone deficiency.
- Phase IV study P0583n, and on-going National Cooperative Growth Study.

Should you have any further questions regarding this submission please contact Mr. Shawn McLaughlin of my staff at (650) 225-1915.

Sincerely,

Allen R. Dodson for

Robert L. Garnick, Ph.D.
Vice President
Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

20522-096 sub ss

Cross-reference:
NDA 19-676, S-016

Genentech, Inc.

1 DNA Way
South San Francisco, CA 94080-4990
(650) 225-1000
FAX (650) 225-6000

ORIGINAL

June 24, 1999

NDA NO. 20-522 REF. NO. 013
NDA SUPPL FOR SLR

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]
Supplement – Labeling
Pubertal Dosing

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}.

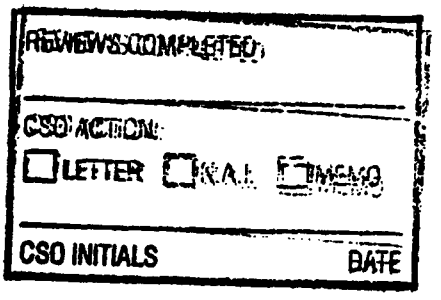
A supplement providing clinical data to support the addition of a higher pubertal dose for pubertal patients to the dosing section of the product insert has been submitted to NDA 19-676 (S-016, submitted June 11, 1999). This Nutropin supplement is therefore cross-referenced and the data contained therein is considered to be applicable to Nutropin AQ, based on the established bioequivalence of the two products. This revised labeling for Nutropin AQ is being submitted concurrently with the labeling supplement for lyophilized Nutropin in order to make possible a simultaneous review of the Pubertal Dosing supplements for both Nutropin and Nutropin AQ.

Enclosed is a revised package insert for Nutropin AQ® [somatropin (rDNA origin) injection] with the bone mineral density claim added. The changes are indicated by underlined text.

Should you have any questions regarding this submission please contact Mr. Shawn McLaughlin of my staff at (650) 225-1915.

Sincerely,

Robert L. Garnick, Ph.D.
Vice President
Regulatory Affairs



20522-093 sub ss

ORIGINAL

SUPPL NEW CORRESP
5E2-013-SNC

Genentech, Inc.

1 DNA Way
South San Francisco, CA 94080-4990
(650) 225-1000
FAX: (650) 225-6000

August 11, 1999

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-013**
Nutropin AQ® [somatropin (rDNA origin) injection]
Labeling Supplement – Pubertal Dosing
Request for Waiver of Requirement to Conduct Pediatric Studies
[21CFR 201.23(a)]

Dear Dr. Sobel:

Reference is made to our Supplemental New Drug Application, NDA 20-522, S-013, for Nutropin AQ® [somatropin (rDNA origin) injection], submitted on June 24, 1999 for the addition of a higher pubertal dose for pubertal patients being treated for growth failure due to a lack of adequate endogenous growth hormone secretion.

Further to a telephone conversation with Crystal King of your office, and in regard to the FDA Final Rule: Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients, we are requesting a waiver from the requirements of 21CFR 201.23(a), under subpart (c)(1), on the basis that adequate pediatric studies have already been performed with Nutropin AQ and Nutropin® [somatropin (rDNA origin) for injection].

20522-096 sub ss

The studies already performed in pediatrics include:

- Study L0368g in NDA 20-522, and studies 86-061 and 87-070 in NDA 19-676, for pediatric growth hormone deficiency.
- Studies 87-069 and M0079g in NDA 20-168, for growth failure associated with chronic renal insufficiency.
- Study 85-044 in NDA 20-656, for short stature associated with Turner syndrome.
- Study M0380g in IND 27,603, for pubertal dosing in pediatric growth hormone deficiency.
- Phase IV study : — , and — National Cooperative Growth Study.

Should you have any further questions regarding this submission please contact Mr. Shawn McLaughlin of my staff at (650) 225-1915.

Sincerely,

Allene B. Dodge for

Robert L. Garnick, Ph.D.
Vice President
Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

20522-096 sub ss