CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

19-676/S-016

Correspondence

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 19-676,** S-016
Nutropin® Pubertal Dosing Supplement
Amendment to a Pending Application
Item 2 – Labeling
Item 4 – Chemistry, Manufacturing, and Controls
Environmental Assessment

Dear Dr. Jenkins:

Genentech, Inc. is submitting the enclosed information to our supplement S-016 to NDA 19-676 for the pubertal dosing regimen of Nutropin [somatropin (rDNA origin) for injection]. For the record, we are submitting an email sent on April 10, 2000 with the final redlined version of the package insert, a clean version of the package insert, and a fax sent to Ms. Enid Galliers on April 6, 2000, following her request for an Environmental Assessment for this supplement. A desk copy is provided in a black binder for Ms. Crystal King, P.D., M.G.A., Project Manager. The review copies have been placed in the appropriate colored binders.

An electronic archival copy of this submission on one CD has been submitted under separate cover to the CDER Central Document Room, according to the Guidance for Industry—Providing Regulatory Submissions in Electronic Format—General Considerations. Text is provided in Adobe Acrobat pdf format.

19676-011 sub rer

For help or information concerning any technical issues associated with the CD or electronic documents, please contact Mr. Scott Moore at (650) 225-7137 or Mr. Jan Van Gelder at (650) 225-1558. 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

19676-011 sub rer

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Genentech, Inc.	April 11, 2000
TELEPHONE NO. *(Include Area Code)* (650) 225-1202	**FACSIMILE (FAX) Number** *(Include Area Code)* (650) 225-1397
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 1 DNA Way South San Francisco, CA 94080-4990	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 19-676, S-016

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
somatropin (rDNA origin) for injection	Nutropin®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
recombinant human growth hormone	

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
lyophilized	5mg vial, 10mg vial	subcutaneous injection

(PROPOSED) INDICATION(S) FOR USE:
growth failure due to a lack of endogenous growth hormone

APPLICATION INFORMATION

APPLICATION TYPE (check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one) ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT ☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION copies of email responses

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 — THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

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

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND

This application contains the following items: *(Check all that apply)*	
	1. Index
X	2. Labeling (check one) ☒ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
X	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 2397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Robert L. Garnick, Ph.D. V.P., Regulatory Affairs	April 11, 2000

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
1 DNA Way, South San Francisco, CA 94080-4990	(650) 225-1202

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address.

LABELING SUPPLEMENT (PUBERTAL DOSING): ITEM 2
Nutropin® [somatropin (rDNA origin) for injection] NDA 19-676, S-016

2. LABELING: APRIL 11, 2000 AMENDMENT

TABLE OF CONTENTS

Subject: Nutropin Revised Pubertal PI
Date: Mon, 10 Apr 2000 18:08:18 -0700
From: Fiona Cameron <cameron2@gene.com>
Organization: Genentech, Inc.
To: Crystal King 301-827-6423 FAX 301-443-9282 <KINGC@cder.fda.gov>, malozowskis@cder.fda.gov, perlsteinr@cder.fda.gov

Encrypted and Signed

Nutropin NDA 19-676_S-016 Pubertal Dosing

Dear All:

Further to our conversation today, attached is a redlined version of the Nutropin package insert showing your requested changes.

We added the mean +/- SD for the mean last measured height for the two groups as requested. Although the mean heights are adjusted for sex and it states so in the text, it may not be clear to the reader whether these values are representative of males, females or some combination of both. The presentation of the mean difference avoids this issue. We look forward to your final decision on this point.

Please let me know as soon as possible whether you are in agreement with these changes, and we will then prepare the final CD for submission.

Best regards
Fiona

	Name: 19-676S016redlinedPI_10APR00.doc **Type:** Winword File (application/msword) **Encoding:**

LABELING SUPPLEMENT (PUBERTAL DOSING): ITEM 4
Nutropin® [somatropin (rDNA origin) for injection] NDA 19-676, S-016

4. CHEMISTRY: APRIL 11, 2000 AMENDMENT

TABLE OF CONTENTS

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 Cameron
cameron2@gene.com

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

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.

Genentech, Inc.

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

March 30, 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 19-676, S-016**
Nutropin® [somatropin (rDNA origin) for injection]
Amendment to a Pending Application—Pubertal Dosing Supplement
Item 2—Labeling

Dear Dr. Jenkins:

Genentech, Inc. is submitting the enclosed information to our supplement S-016 to NDA 19-676 for the pubertal dosing regimen of Nutropin [somatropin (rDNA origin) for injection]. For the record, we are submitting emails that have been sent to the reviewers during the package insert negotiations. We are also including the final version of both the redlined and clean package insert showing the new text. 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 review copies have been placed in the appropriate colored binders.

In addition, as a Phase IV commitment, 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.

19676-110 sub rer

- 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)
  We will include an indication that the patient was being dosed at greater than or equal to 0.4 mg/kg at the beginning of the narrative of any relevant expedited adverse event reports, and will also include this information in the cover letter that accompanies each of these reports.

An electronic archival copy of this submission on one CD has been submitted under separate cover to the CDER Central Document Room, according to the Guidance for Industry—Providing Regulatory Submissions in Electronic Format—General Considerations. Text is provided in Adobe Acrobat PDF format.

For help or information concerning any technical issues associated with the CD or electronic documents, please contact Mr. Scott Moore at (650) 225-7137 or Mr. Jan Van Gelder at (650) 225-1558. 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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Genentech, Inc.	March 30, 2000
TELEPHONE NO. *(Include Area Code)* (650) 225-1202	**FACSIMILE (FAX) Number** *(Include Area Code)* (650) 225-1397
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 1 DNA Way South San Francisco, CA 94080-4990	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 19-676, S-016

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
somatropin (rDNA origin) for injection	Nutropin®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
recombinant human growth hormone	

DOSAGE FORM	STRENGTHS:	ROUTE OF ADMINISTRATION:
lyophilized	5mg vial, 10mg vial	subcutaneous injection

(PROPOSED) INDICATION(S) FOR USE:
growth failure due to a lack of endogenous growth hormone

APPLICATION INFORMATION

APPLICATION TYPE (check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

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IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

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NUMBER OF VOLUMES SUBMITTED 1 — THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

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

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	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

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2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Robert L. Garnick	Robert L. Garnick, Ph.D. V.P., Regulatory Affairs	March 30, 2000

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
1 DNA Way, South San Francisco, CA 94080-4990	(650) 225-1202

1. INDEX: MARCH 30, 2000 AMENDMENT

LABELING SUPPLEMENT (PUBERTAL DOSING): **ITEM 2**
Nutropin® [somatropin (rDNA origin) for injection] **NDA 19-676, S-016**

2. LABELING: MARCH 30, 2000 AMENDMENT

TABLE OF CONTENTS

Subject: Nutropin Pubertal Dosing Submission Q&A
Date: Thu, 10 Feb 2000 07:49:55 -0800
From: Fiona Cameron <cameron2@gene.com>
Organization: Genentech, Inc.
To: kingc@cder.fda.gov, perlsteinr@cder.fda.gov

Encrypted and Signed

Nutropin NDA 19-676, S-016
Responses to Questions asked By Dr. Perlstein on 1/28/00

Dear Dr. Perlstein and Crystal:

Attached are Genentech's responses to the questions Dr. Perlstein asked Ken Attie on 1/28/00 regarding our Nutropin pubertal dosing submission. The following files are attached:

Clinical.pdf - this contains the questions and answers in a .pdf format.

19676S016PI_09FEB00.doc - a marked up copy of the package insert in Word, showing revisions to the pubertal efficacy information (red text) which were inadevertently omitted from the Novemeber update submission, as well as the new BMD information which was recently approved (blue text).

19676S016cleanPI_09FEB00.doc - a clean version of the package insert also in Word.

I propose that we send you our correspondence to this supplement via email, and then at the end of the process we can compile the electronic archival CD with all of the correspondence, similar to how we did it for Nutropin Depot. Please let me know if this is not acceptable.

I expect to have the responses to the questions Sue-Jane had by the end of this week.

Hope things are going well for you both - please let me know if there are any problems with this email.
Best regards
Fiona

19-676S016cleanPI_09FEB00.doc	**Name:** 19-676S016cleanPI_09FEB00.doc **Type:** Winword File (application/msword) **Encoding:**

19-676S016PI_09FEB00.doc	**Name:** 19-676S016PI_09FEB00.doc **Type:** Winword File (application/msword) **Encoding:**

clinical.pdf	**Name:** clinical.pdf **Type:** Acrobat (application/pdf) **Encoding:**

Subject: 19-676-016 labeling
Date: Wed, 22 Mar 2000 10:49:22 -0500 (EST)
From: "Crystal King 301-827-6423 FAX 301-443-9282" <KINGC@cder.fda.gov>
To: "Fiona Cameron" <cameron2@gene.COM>
CC: "Crystal King" <KINGC@cder.fda.gov>

Encrypted and Signed

Fiona:
Attached is our label version for discussion. Please call us at 2pm EST at 301-827-6434.
Thanks,
Crystal

C:\MYDOCU~1\NDA\N19676\N19676\PUBERT~1\LABELING.DOC	**Name:** C:\MYDOCU~1\ND **Type:** Winword File (appl **Encoding:**

Subject: Nutropin NDA 19-676, Pubertal Dosing Package Insert
Date: Wed, 22 Mar 2000 19:06:47 -0800
From: Fiona Cameron <cameron2@gene.com>
Organization: Genentech, Inc.
To: kingc@cder.fda.gov, malozowskis@cder.fda.gov, perlsteinr@cder.fda.gov, wangs@cder.fda.gov, sahlroott@cder.fda.gov

Encrypted and Signed

Nutropin NDA 19-676, S-016, Pubertal Dosing

Dear All:

Attached for your review is our revised draft of the package insert based on our discussion today (changes shown in revisions mode). Please note the following:

Efficacy
Our proposed wording is provided for your consideration.

IGF-I Levels
We have proposed the weighted average method of making the statement about the number of patients who experienced IGF-I levels above normal. However, we are willing to discuss this further.

Patients Discontinuing From the Study
The number of patients listed as having discontinued because they were satisfied with height is now given as 11 (revised from 9) in the 0.7 mg/kg/wk group. After a review of the listings, two patients were identified as having cited this as the reason (in addition to other reasons which were then given as the discontinuation reason in the database). These additional two patients are as follows:

23-703 lists "PT & PARENT SATIS HT" (see page 7 of the email submission to Sue Jane Wang dated 2/10/00, file clinical2.pdf)

159-223 lists "PATIENT WISHES TO STOP THE GROWTH HORMONE THERAPY AS HE HAS REACHED QUITE A SUBSTANTIAL HEIGHT" (page 9, ibid)

We are confirming management approval of our Phase IV commitment proposal, and hope to confirm that in writing via email as requested tomorrow.

Please let me know if there are any problems with the attached file.
Thanks for your help, and look forward to talking with you again on Friday.
Best regards
Fiona

FromGNE032200.doc	Name: FromGNE032200.doc Type: Winword File (application/msword) Encoding:

Subject: Nutropin Pubertal Dosing Supplement - PI Revisions
Date: Thu, 23 Mar 2000 19:06:59 -0800
From: Fiona Cameron <cameron2@gene.com>
Organization: Genentech, Inc.
To: Crystal King 301-827-6423 FAX 301-443-9282 <KINGC@cder.fda.gov>, malozewskis@cder.fda.gov, perlsteinr@cder.fda.gov, wangs@cder.fda.gov, sahlroott@cder.fda.gov

Encrypted and Signed

Nutropin NDA 19-676, S-016 Pubertal Dosing

Dear All:

Further to Dr. Perlstein's telecon with Ken Attie today, we are providing some additional proposals for revisions to the pubertal dosing section of the Nutropin package insert, attached as a word document.

We are including our proposed Phase IV commitment in writing as requested, also as a word document.

We look forward to talking with you again tomorrow Friday at 1pm your time (please let me know if there are any changes to this time, as we can be flexible). We will call you at 301 827 6434.

Thanks and best regards
Fiona

FromGNE032300.doc	**Name:** FromGNE032300.doc **Type:** Winword File (application/msword) **Encoding:** base64

PubPhaseIVCmt.doc	**Name:** PubPhaseIVCmt.doc **Type:** Winword File (application/msword) **Encoding:**

Subject: Nutropin NDA 19-676 Pubertal Dosing Package Insert
Date: Fri, 24 Mar 2000 22:12:10 -0800
From: Fiona Cameron <cameron2@gene.com>
Organization: Genentech, Inc.
To: Crystal King 301-827-6423 FAX 301-443-9282 <KINGC@cder.fda.gov>, malozowskis@cder.fda.gov, peristeinr@cder.fda.gov, wangs@cder.fda.gov, sahlroott@cder.fda.gov

Encrypted and Signed

Nutropin NDA 19-676 Pubertal Dosing Supplement S-016

Dear All:

Further to our discussion today, attached are the following:

Revised Package Insert sections (FromGNE032400.doc)

Additional statistical information on ANCOVA analyses for Dr. Sahlroot (ANCOVAdata.doc)

Regarding the request for medians, below is information regarding percentage of IGF-I measurements above the normal range for individuals at various percentiles:

	0.3	0.7
25%ile	0%	0%
50%ile	0 %	17%
75%ile	14 %	44%

Look forward to talking to you again at ~11.15am your time on Monday.
Best regards
Fiona

ANCOVAdata.doc	**Name:** ANCOVAdata.doc **Type:** Winword File (application/msword) **Encoding:** base64

FromGNE032400.doc	**Name:** FromGNE032400.doc **Type:** Winword File (application/msword) **Encoding:**

Subject: Nutropin Pubertal Dosing - PI Revision
Date: Wed, 29 Mar 2000 18:31:18 -0800
From: Fiona Cameron <cameron2@gene.com>
Organization: Genentech, Inc.
To: Crystal King 301-827-6423 FAX 301-443-9282 <KINGC@cder.fda.gov>, malozowskis@cder.fda.gov, perlsteinr@cder.fda.gov, wangs@cder.fda.gov, sahlroott@cder.fda.gov

Encrypted and Signed

Nutropin NDA 19-676, S-013, Pubertal Dosing Supplement

Dear All:

Attached are the revisions to the package insert based on our discussions today. An explanation of some of the edits we made is provided below.

1. We added age to the table since being an intent to treat analysis, several subjects who discontinued early were quite young and we are showing height and not height SDS.

2. We used SD for mean last measured height because we feel this best describes the variance of the population in addition to being a parameter that prescribers are most familiar with. We would be willing to put the 95% CI in, although this was deleted elsewhere in the text.

3. The use of standardized height in the 2nd ANCOVA analysis gave us a meaningless result, probably because this introduces a lot of confounding information. We therefore ran the ANCOVA using just baseline height and adding sex as a second covariate, which best approximates the previous ANCOVA where baseline height was used and the results were reported by sex. The difference was statistically significant.

Please let us know when you would like to discuss this again.
Best regards and thank you for your help
Fiona

From GNE032900.doc	**Name:** From GNE032900.doc **Type:** Winword File (application/msword) **Encoding:**

Subject: Nutropin NDA 19-676 Pubertal Final Label
Date: Thu, 30 Mar 2000 13:18:17 -0800
From: Fiona Cameron <cameron2@gene.com>
Organization: Genentech, Inc.
To: Crystal King 301-827-6423 FAX 301-443-9282 <KINGC@cder.fda.gov>

Encrypted and Signed

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

Dear Crystal:

Attached per your request are the following:

Clean version of the final package insert for Nutropin, including the pubertal dosing information that we sent to you on 3/29/00 (19676cleanPI_30MAR00)

Electronic copy of the cover letter containing our Phase IV commitment (19676finalcover.doc)

I will fax you the requested information (signed cover letter, ToCs, Final Label) later today.

Thanks again for your help
Best regards
Fiona

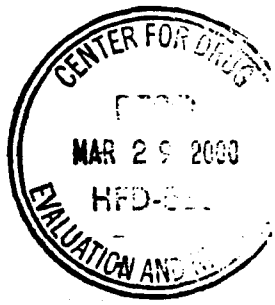
19676finalcover.doc	**Name:** 19676finalcover.doc **Type:** Winword File (application/msword) **Encoding:**

19-676S016cleanPI_30MAR00.doc	**Name:** 19-676S016cleanPI_30MAR00.doc **Type:** Winword File (application/msword) **Encoding:**

Genentech, Inc.

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

March 27, 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 19-676, S-016**
Nutropin® [somatropin (rDNA origin) for injection]
Amendment to a Pending Application—Pubertal Dosing Supplement
Item 8 – Clinical Section
Item 11 – Case Report Tabulations
Item 19 – Other

Dear Dr. Jenkins:

Genentech, Inc. is submitting the enclosed information to our supplement S-016 to NDA 19-676 for the pubertal dosing regimen of Nutropin [somatropin (rDNA origin) for injection]. For the record, we are submitting emails that have been sent to the reviewers in response to their questions with respect to Items 8 and 11. We are also including complete information regarding investigator financial disclosure under Item 19. This section was inadvertently incomplete in the original submission submitted on June 11, 1999. 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 review copies have been placed in the appropriate colored binders.

An electronic archival copy of this submission on one CD has been submitted under separate cover to the CDER Central Document Room, according to the Guidance for Industry – Providing Regulatory Submissions in Electronic Format – General Considerations. Text is provided in Adobe Acrobat pdf format.

19676-109 sub ss

For help or information concerning any technical issues associated with the CD or electronic documents, please contact Mr. Scott Moore at (650) 225-7137 or Mr. Jan Van Gelder at (650) 225-1558.

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 supplement. We look forward to working with you during your review of this information.

Sincerely,

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

19676-109 sub ss

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Genentech, Inc.	March 27, 2000
TELEPHONE NO. *(Include Area Code)* (650) 225-1202	**FACSIMILE (FAX) Number** *(Include Area Code)* (650) 225-1397
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 1 DNA Way South San Francisco, CA 94080-4990	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 19-676, S-016

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
somatropin (rDNA origin) for injection	Nutropin®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*	CODE NAME *(If any)*
recombinant human growth hormone	

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
lyophilized	5mg vial, 10mg vial	subcutaneous injection

(PROPOSED) INDICATION(S) FOR USE:
growth failure due to a lack of endogenous growth hormone

APPLICATION INFORMATION

APPLICATION TYPE (check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94) ☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one) ☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT
☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION copies of email responses

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 — THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

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

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
X	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case report forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k)(1))
	17. Field copy certification (21 CFR 314.50 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
X	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been review and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
[signature]	Robert L. Garnick, Ph.D. V.P., Regulatory Affairs	March 27, 2000

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
1 DNA Way, South San Francisco, CA 94080-4990	(650) 225-1202

LABELING SUPPLEMENT (PUBERTAL DOSING): ITEM 1

Nutropin® [somatropin (rDNA origin) for injection] NDA 19-676, S-016

1. INDEX: MARCH 27, 2000 AMENDMENT

LABELING SUPPLEMENT (PUBERTAL DOSING): ITEM 8
Nutropin® [somatropin (rDNA origin) for injection] NDA 19-676, S-016

8. CLINICAL DATA: MARCH 27, 2000 AMENDMENT

TABLE OF CONTENTS

Subject: Nutropin Pubertal Dosing Submission Q&A
Date: Thu, 10 Feb 2000 07:49:55 -0800
From: Fiona Cameron <cameron2@gene.com>
Organization: Genentech, Inc.
To: kingc@cder.fda.gov, perlsteinr@cder.fda.gov

Encrypted and Signed

Nutropin NDA 19-676, S-016
Responses to Questions asked By Dr. Perlstein on 1/28/00

Dear Dr. Perlstein and Crystal:

Attached are Genentech's responses to the questions Dr. Perlstein asked Ken Attie on 1/28/00 regarding our Nutropin pubertal dosing submission. The following files are attached:

Clinical.pdf - this contains the questions and answers in a .pdf format.

19676S016PI_09FEB00.doc - a marked up copy of the package insert in Word, showing revisions to the pubertal efficacy information (red text) which were inadevertently omitted from the Novemeber update submission, as well as the new BMD information which was recently approved (blue text).

19676S016cleanPI_09FEB00.doc - a clean version of the package insert also in Word.

I propose that we send you our correspondence to this supplement via email, and then at the end of the process we can compile the electronic archival CD with all of the correspondence, similar to how we did it for Nutropin Depot. Please let me know if this is not acceptable.

I expect to have the responses to the questions Sue-Jane had by the end of this week.

Hope things are going well for you both - please let me know if there are any problems with this email.
Best regards
Fiona

19-676S016cleanPI_09FEB00.doc	**Name:** 19-676S016cleanPI_09FEB00.doc **Type:** Winword File (application/msword) **Encoding:**

19-676S016PI_09FEB00.doc	**Name:** 19-676S016PI_09FEB00.doc **Type:** Winword File (application/msword) **Encoding:**

clinical.pdf	**Name:** clinical.pdf **Type:** Acrobat (application/pdf) **Encoding:**

2/10/00 4:45 PM

27MAR2000

Subject: Nutropin Pubertal Dosing - Sue Jane's Questions
Date: Thu, 10 Feb 2000 17:05:01 -0800
From: Fiona Cameron <cameron2@gene.com>
Organization: Genentech, Inc.
To: kingc@cder.fda.gov

Encrypted and Signed

Nutropin NDA 19-676 S-016
Pubertal Dosing

Dear Crystal:

Attached are the responses to the questions that you and Sue-Jane Wang discussed with me on 2/7/00. If you could forward these to Sue Jane I would be grateful. Two files are attached:

clinical2.pdf - contains the questions and responses in pdf format

disp380.xpt - a SAS transport file containing a patient disposition dataset

I hope that these address Sue Jane's questions, we had already prepared these responses when we got the request email from you today. If there is any further clarification needed, please let me know and we will provide whatever is needed.

Best regards
Fiona

disp380.xpt	**Name:** disp380.xpt **Type:** application/x-sas-xport **Encoding:**

clinical2.pdf	**Name:** clinical2.pdf **Type:** Acrobat (application/pdf) **Encoding:**

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

FAX COVER SHEET

Regulatory Affairs Department
One DNA Way
South San Francisco, CA 94080-4990
(650) 225-1915
TWX: 9103717168
FAX: (650) 225-1397

FAX NUMBER: (301) 443-9282

DATE: February 18, 2000

TO: Crystal King, P.D., M.G.A (301) 827-6423

FROM: Shawn McLaughlin, M.B.A., Regulatory Affairs (650) 225-1915

NUMBER OF PAGES: 68 (including this page)

Dear Crystal:

Please reference our Nutropin® Supplement for Pubertal Dosing, NDA 19-676, S-016, and Sue-Jane Wang's 2/13/00 request for additional information. Attached is a copy of the information we FedEx'd to her this afternoon. She specifically requested that the information be sent directly to her, to arrive tomorrow.

As previously discussed, we will prepare and submit an update to the electronic, archival file for NDA 19-676, S-016 this coming week, which compiles all the most recent requests from review activities.

Best regards,

Shawn D. McLaughlin
Senior Associate
Regulatory Affairs

Genentech, Inc.

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

February 18, 2000

Sue-Jane Wang, Ph.D.
Senior Statistician
Center for Drug Evaluation and Research
Food and Drug Administration
PKLN 9B07, HFD-715
5600 Fishers Lane
Rockville, MD 20857

Subject: NDA 19-676, S-016
Response to request for information

Dear Dr. Wang:

Reference is made to our Supplemental New Drug Application, NDA 19-676, S-016, for Nutropin® [somatropin (rDNA origin) for injection], submitted June 11, 1999, providing clinical data to support 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. Additionally, the Final report for this study was submitted November 19, 1999. This document provides the additional information as specified in your February 13, 2000 request, and as discussed in our teleconference on February 16.

(1) SAS dataset of disp380.xpt and prim380b.xpt, both with the extrapolation indicator (requirement of bone age to be extrapolated to the date of subjects' last measured height).

(2) An annotated CRF with SAS variable names listed in the three files submitted (prim_380.xpt, sec_380.xpt, else_380.xpt) and those variables used for analyses in Section 5 up to 5.3 (p.29-p.46) of the NDA jacket 52.1.

(3) Statistical analysis outputs along with statistical tests (not data listings) for Figures 1 to 8 in the text and Tables 3 to 7 in Appendix.

Enclosed is a paper copy of the document as well as a zip disk containing data files. As previously agreed upon by Ms. Crystal King, Project Manager, we will follow-up with submission of a compiled update to the archival electronic

supplement 19-676, S-016 that includes all the most recent responses for information.

We hope you find this information helpful and sufficient for your needs. If you require anything further, please contact me at (650) 225-1915, fax: (650) 225-1397, or internet: shawn@gene.com.

Sincerely,

Shawn D. McLaughlin
Senior Associate
Regulatory Affairs

cc: Crystal King, P.D., M.G.A.

Subject: Re: [Fwd: Re: Nutropin Pubertal Dosing]
Date: Tue, 29 Feb 2000 14:26:49 -0800
From: Joyce Baptista <baptista@gene.COM>
Organization: Genentech, Inc.
To: WANGS@cder.fda.gov
CC: Peggy Wooster <wooster@gene.COM>, shawn@gene.COM, KINGC@cder.fda.gov, Fiona Cameron <cameron.fiona@gene.COM>, Scott Moore <moore.scott@gene.COM>, "attie.kenneth" <attie.kenneth@gene.COM>

Ms. Wang,

We spoke on a telecom not long ago regarding the Nutropin pubertal dosing submission. I am the statistician who worked on the interim report for M0380g. Your last email was forwarded to me. Attached is my response. I hope you find it helpful. If you have any questions please let us know.

Thank you.

JB

Peggy Wooster wrote:

> -------- *Original Message* --------
> *Subject: Re: Nutropin Pubertal Dosing*
> *Date: Mon, 28 Feb 2000 11:52:31 -0500 (EST)*
> *From: "Sue Jane Wang 301-827-7435 FAX 301-827-5875" <WANGS@cder.fda.gov>*
> *To: "Fiona Cameron" <cameron.fiona@gene.COM>, "Peggy Wooster"*
> *<wooster.peggy@gene.COM>*
> *CC: "Shawn McLaughlin" <shawn@gene.COM>, "Crystal King"*
> *<KINGC@cder.fda.gov>*
>
> *Hi Fiona and Peggy,*
>
> *I just sent an email to Shawn and learned that he won't be in until*
> *March 1, 2000. So, I am forwarding the email to you both.*
>
> *If you have any questions, I can be reached at (301)827-3089.*
>
> *Thanks, Sue-Jane*
>
> ---
>
> *Subject: Re: Nutropin Pubertal Dosing*
> *Date: Mon, 28 Feb 2000 11:46:25 -0500 (EST)*
> *From: "Sue Jane Wang 301-827-7435 FAX 301-827-5875" <WANGS@cder.fda.gov>*
> *To: "Shawn McLaughlin" <shawn@gene.com>*
> *CC: "Crystal King" <KINGC@cder.fda.gov>*
>
> *Shawn,*
>
> *There were 13 subjects who reached the adult height.*
>
> *Please provide the following information today if possible.*
>
> *(1) patient IDs of these subjects.*
>
> *(2) sample size, mean, median, sd, range of baseline height and adult*
> *height for the low dose and high dose separately.*
>
> *Thanks,*

Re: [Fwd: Re: Nutropin Pubertal Dosing]

>
> Sue-Jane

Sue Jane Wang 2.doc	**Name:** Sue Jane Wang 2.doc **Type:** Winword File (application/msword) **Encoding:** **Download Status:** Not downloaded with message

Subject: Nutropin Pubertal Dosing NDA 19-676 S-016 Q&A
Date: Thu, 02 Mar 2000 19:05:09 -0800
From: Fiona Cameron <cameron2@gene.com>
Organization: Genentech, Inc.
To: kingc@cder.fda.gov, perlsteinr@cder.fda.gov

Encrypted and Signed

Nutropin NDA 19-676, S-016 Pubertal Dosing
Responses to Questions asked by Dr. Perlstein on 2/25/00

Dear Dr. Perlstein and Crystal:

Attached are Genentech's responses to the questions Dr. Perlstein asked Ken Attie on 2/25/00 regarding our Nutropin pubertal dosing submission. The following files are attached:

clinical_3.pdf (Questions derived from telephone call and our responses)

Table_02.doc (Word table as requested, also provided as .pdf in response to Question 4)

Please let me know if you have any problems with these files.
Thanks and best regards
Fiona

clinical_3.pdf	**Name:** clinical_3.pdf **Type:** Acrobat (application/pdf) **Encoding:**

Table_02.doc	**Name:** Table_02.doc **Type:** Winword File (application/msword) **Encoding:**

Subject: Nutropin Pubertal Dosing NDA 19-676, S-016 Q&A
Date: Mon, 06 Mar 2000 18:36:10 -0800
From: Fiona Cameron <cameron2@gene.com>
Organization: Genentech, Inc.
To: kingc@cder.fda.gov, perlsteinr@cder.fda.gov

Encrypted and Signed

Dear Crystal and Dr. Perlstein:
Attached below are Genentech's responses to two questions asked by Dr. Perlstein on 3/3/00.
Best regards
Fiona

Nutropin Pubertal Dosing Submission, NDA 19-676, S-016
Responses to Dr Perlstein's Questions from 3/3/00 Telecon

1. When were the pretreatment growth rate measurements performed?

Previous height and date measured were recorded on the screening visit Case Report Form, which stipulates "at least 6 months prior to enrollment" (refer to submission dated November 19, 1999, page 444). For the 97 subjects enrolled, the range of days from date of previous height measurement was actually 70 to 511 days (mean 296 days) which is close to the range used in the Nutropin Depot study of 60 to 425 days. For the 3 patients in the pubertal dosing study whose previous height date was less than 5 months, the previous growth rate was set to "missing" and hence n=94 for previous growth rate in Table 4 - Demographics and Baseline Characteristics of the November 19, 1999 submission, page 32. Annualized baseline growth rates were calculated.

2. Were patients with the following disorders/concomitant medications excluded from the study:
Diabetes mellitus
Hypothalamic pituitary tumors diagnosed within one year of enrollment
Allergy to components of the drug
Known bleeding disorder
Current treatment with methylphenidate or cryptoheptadine

A review of the baseline adverse events patient listings indicates that no patients with diabetes mellitus or known bleeding disorders entered the trial. With respect to pituitary tumors, one of the exclusion criteria was "patient has a history of malignancy diagnosed and/or has been treated within the past year" (refer to screening CRF in the submission of November 19, 1999, page 443). Although allergy to components of the drug was not a specific exclusion criterion, no allergic reactions to the drug were noted. Patients being treated with methylphenidate (Ritalin®) or cyproheptadine (Periactin®) were permitted to be included in the study, as many adolescents are treated with these drugs and this facilitated recruitment.

3/6/00 6:37 PM

27MAR2000

ech, Inc.

CA 94080-4990

November 19, 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 19-676, S-016**
Nutropin® [somatropin (rDNA origin) for injection]
Labeling Supplement – Pubertal Dosing
Safety Update/Final Report

Dear Dr. Sobel:

Reference is made to our Supplemental New Drug Application, NDA 19-676, S-016, for Nutropin® [somatropin (rDNA origin) for injection], submitted on June 11, 1999, providing clinical data to support the addition of a higher dose for pubertal patients being treated for growth failure due to a lack of adequate endogenous growth hormone secretion. In accordance with 21 CFR 314.50(d)(5)(vi)(b), this submission provides the "four month" safety update. In addition, this submission contains Patent Information (Item 13) and Patent Certification (Item 14), which was not included in the original supplement, but was subsequently requested by the Agency.

As agreed to in a telephone conversation with Ms. Crystal King, FDA Project Manager, on September 15, 1999, the Final Report for study M0380g: A Phase III, Randomized, Multicenter Study of Nutropin Treatment at Two Dosage Levels In Pubertal Children with GHD, is being submitted as the Safety Update for this labeling supplement.

As this is a final report, both the efficacy and safety sections have been updated to include complete data for the study. As such, all sections of the interim report, submitted with the original application NDA 19-676, S-016, can be considered superseded by this final report. Since the major efficacy outcomes are essentially the same as discussed in the interim report, this is not intended as a submission of new efficacy data, as discussed with Ms. King.

Please note that in a few instances, the number of subjects with certain adverse events are less compared to the interim report. These changes are due to the following corrections to the database: 1) Four subjects with added baseline information resulting in event no longer being emergent. 2) Two subjects with correction of AE severity resulting in no change from baseline. 3) One subject with corrected mapping of AE to COSTART term. 4) One subject with correction (deletion) of AE.

This submission does not contain revised labeling, as the data collected during the update period is consistent with that seen earlier in the trial, and with the current draft labeling.

An electronic archival copy of this submission on CD-ROM has been submitted to the CDER Central Document Room, according to the Guidance for Industry- Providing Regulatory Submissions in Electronic Format- General Considerations. Text is provided in Adobe Acrobat pdf format. Patient listings and datasets are provided in electronic form only. The CD has been checked for computer viruses using Norton AntiVirus for Windows NT Workstation 5.01.01a (with virus definitions dated 9/22/99), and is hereby certified to be virus-free.

Should you have any further 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

19676-105 sub ss

DUPLICATE

Genentech, Inc.

SUPPL NEW CORRESP
SE 8-016-SNC

1 DNA Way
South San Francisco, CA 94080-4990
650 225 1000
FAX 650 225-8506

August 11, 1999

CENTER FOR DRUG
REC'D
AUG 13 1999
HFD-510
EVALUATION AND RESEARCH

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 19-676, S-016**
Nutropin® [somatropin (rDNA origin) for 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 19-676, S-016, for Nutropin® [somatropin (rDNA origin) for injection], submitted on June 11, 1999 providing clinical data to support 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.

19676-099 sub ss

The studies already performed in pediatrics include:

- Studies 86-061 and 87-070 in NDA 19-676, for pediatric growth hormone deficiency.
- Studies 87-069, M0079g, and M0221g 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 [redacted] for pubertal dosing in pediatric growth hormone deficiency.
- Phase IV study [redacted]

Should you have any further 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

19676-099 sub ss

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Genentech, Inc.	**August 11, 1999**
TELEPHONE NO. *(Include Area Code)* **(650) 225-1202**	FACSIMILE (FAX) Number *(Include Area Code)* **(650) 225-1397**
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* **1 DNA Way South San Francisco, California, USA 94080-4990 License 1048**	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE*

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) **NDA 19-676, S-016**

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY	
somatropin (rDNA origin) for injection	**Nutropin®**	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* **recombinant human growth hormone**		CODE NAME *(If any)*
DOSAGE FORM: **lyophilized**	STRENGTHS: **5mg vial,10mg vial**	ROUTE OF ADMINISTRATION: **subcutaneous injection**

(PROPOSED) INDICATION(S) FOR USE:
growth failure due to a lack of endogenous growth hormone

APPLICATION INFORMATION

APPLICATION TYPE (check one)
■ NEW DRUG APPLICATION (21 CFR 314.50) □ ABBREVIATED APPLICATION (ANDA, AADA, 21CFR 314.94)
□ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ■ 505 (b) (1) □ 505 (b) (2) □ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
□ ORIGINAL APPLICATION □ AMENDMENT TO A PENDING APPLICATION □ RESUBMISSION
□ PRESUBMISSION □ ANNUAL REPORT □ ESTABLISHMENT DESCRIPTION SUPPLEMENT □ SUPAC SUPPLEMENT
□ EFFICACY SUPPLEMENT □ LABELING SUPPLEMENT □ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ■ OTHER

REASON FOR SUBMISSION
Request for Waiver of Requirement to Conduct Pediatric Studies

PROPOSED MARKETING STATUS (check one) ■ PRESCRIPTION PRODUCT (Rx) □ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ■ PAPER □ PAPER AND ELECTRONIC □ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

GENENTECH, INC.
1 DNA WAY
SOUTH SAN FRANCISCO, CALIFORNIA 94080-4990

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs refer referenced in the current application)

This application contains the following items: *(Check all that apply)*	
	1. Index
	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry Section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2)
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2)
	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
	16. Debarment certification (FD&C Act 306 (k) (1))
	17. Field copy certification (21 CFR 314.5 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80,314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Robert L. Garnick, Ph.D., Vice President, Regulatory Affairs	**August 11, 1999**

ADDRESS *(Street, City, State, and ZIP code)*	Telephone Number
1 DNA Way, South San Francisco, CA 94080-4990	**(650) 225-1202**

Public reporting burden for this collection of information is estimated to average 40 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS, Reports Clearance Officer
Paperwork Reduction Project (0910-0338)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

Please **DO NOT RETURN** this form to this address

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

June 24, 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**
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.

20522-093 sub ss

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Genentech, Inc.	June 24, 1999
TELEPHONE NO. *(Include Area Code)* (650) 225-1202	**FACSIMILE (FAX) Number** *(Include Area Code)* (650) 225-1397
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 1 DNA Way South San Francisco, California, USA 94080-4990 License 1048	**AUTHORIZED U.S. AGENT NAME & ADDRESS** *(Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE*

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 20-522

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
somatropin (rDNA origin) injection	Nutropin AQ®

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)*: recombinant human growth hormone

CODE NAME *(If any)*:

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
liquid	10 mg vial	subcutaneous injection

(PROPOSED) INDICATION(S) FOR USE:
growth failure due to a lack of endogenous growth hormone

APPLICATION INFORMATION

APPLICATION TYPE (check one)
■ NEW DRUG APPLICATION (21 CFR 314.50) □ ABBREVIATED APPLICATION (ANDA, AADA, 21CFR 314.94)
□ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ■ 505 (b) (1) □ 505 (b) (2) □ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION (check one)
□ ORIGINAL APPLICATION □ AMENDMENT TO A PENDING APPLICATION □ RESUBMISSION
□ PRESUBMISSION □ ANNUAL REPORT □ ESTABLISHMENT DESCRIPTION SUPPLEMENT □ SUPAC SUPPLEMENT
□ EFFICACY SUPPLEMENT ■ LABELING SUPPLEMENT □ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT □ OTHER

REASON FOR SUBMISSION
To add additional pubertal dose to label

PROPOSED MARKETING STATUS (check one) ■ PRESCRIPTION PRODUCT (Rx) □ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ■ PAPER □ PAPER AND ELECTRONIC □ ELECTRONIC

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Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

GENENTECH, INC.
1 DNA WAY
SOUTH SAN FRANCISCO, CALIFORNIA 94080-4990

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs refer referenced in the current application)

19-676, IND [redacted]

This application contains the following items: *(Check all that apply)*	
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X	2. Labeling (check one) ☒ Draft Labeling ☐ Final Printed Labeling
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	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2) ITEM 8.E: Phase I and II Final Reports
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
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	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2)
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	17. Field copy certification (21 CFR 314.5 (k) (3))
	18. User Fee Cover Sheet (Form FDA 3397)
	19. OTHER (Specify)

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80,314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Robert L. Garnick, Ph.D., Vice President, Regulatory Affairs	June 24, 1999

ADDRESS *(Street, City, State, and ZIP code)*	Telephone Number
1 DNA Way, South San Francisco, CA 94080-4990	(650) 225-1202

ORIGINAL

Genentech, Inc.

NDA NO. 19-676 REF NO. 016
NDA SUPPL FOR SE2

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

June 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

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
JUN 14 1999
HFD-510

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Subject: **NDA 19-676**
Nutropin® [somatropin (rDNA origin) for injection]
Supplement - Labeling
Pubertal Dosing

Dear Dr. Sobel:

Reference is made to our New Drug Application, NDA 19-676, for Nutropin® [somatropin (rDNA origin) for injection], approved on March 8, 1994 for treatment of growth failure due to a lack of endogenous growth hormone (GH). This submission provides a clinical data supplement to support the addition of a higher pubertal dose for pubertal patients to the dosing section of the product insert.

Genentech study M0380g, a Phase III, Randomized, Multicenter Study of Nutropin Treatment at Two Dosage Levels in Pubertal Children with GHD was undertaken to investigate the hypothesis that the replacement dose of growth hormone should be approximately doubled during puberty to emulate the physiologic increase normally seen at this time. The Division stated in a letter dated August 9, 1994 (copy included in this submission) that this single study will be sufficient to support this new dosing regimen. In this study, pubertal subjects were randomized to standard (0.3 mg/kg/wk) versus high dose (0.7 mg/kg/wk)

GH and followed to near-adult height. Although standard GH therapy can result in mean adult heights within the normal range, adult heights are typically less than the respective target heights, possibly due to an inadequate pubertal growth spurt.

Adolescence is a time when GH and IGF-I levels are at their highest and sensitivity to GH is at its lowest. The objective of this study was to show that the higher dose is well tolerated, safe, and effective in improving adult height. Patients who were diagnosed or treated late, were inadequately treated, are far below the normal range for height, are growing poorly, have low IGF-I levels, or a combination of the above, may benefit from the relatively short course (2-5 years) of higher dose GH.

Adolescence is also a time of maximal bone mass accrual, coinciding with the time of maximal GH secretion. It has been shown that GH deficiency in childhood can reduce the peak bone mass attained, resulting in premature osteopenia or osteoporosis, despite GH replacement therapy. A secondary goal of the study is to determine the effect of GH dose during puberty on bone mineral density at the end of therapy. DEXA scan data will be summarized in the final report upon completion of the study.

Genentech proposes that the standard dose of 0.3 mg/kg/wk be recommended for all pediatric patients, but that a dose of up to 0.7 mg/kg/wk may be used in pubertal patients, at the discretion of the treating physician, and that IGF-I levels can be monitored to optimize dosing and avoid excess GH exposure. A paragraph describing study M0380g would also be included in the label.

This submission includes an interim report for study M0380g, at a point where approximately two-thirds of the subjects had reached near-adult height, based on the protocol-defined bone age criterion for treatment discontinuation. The primary endpoint specified in the protocol was "adult height", defined as epiphyseal fusion and no growth. In retrospect, it was unreasonable to expect most of these subjects to meet this criteria for quite some time, as evidenced by only a handful of subjects meeting the criteria at this time.

We elected to submit the data now based on the fact that over 80% of subjects had discontinued treatment and 66% achieved near-adult height. Because bone age progressed equally in both groups and was similar at baseline, the last measured heights could be used to compare the two dose groups.

An intent-to-treat analysis was also performed for all 97 subjects using the last measured heights. The analyses performed (ANCOVA) were as specified in the protocol. Since the magnitude of the difference between groups for the effect on adult height increases with continued treatment, the effects reported in this interim report are considered conservative with respect to the impact of the higher dose. Thus, we expect the final data from this study to show even greater gains in the high-dose group than that contained in the interim report.

In addition to improving near-adult height, the higher dose produced significant improvements in growth rate, height SDS, predicted height, and change in height, while having no adverse effect on the rate of pubertal progression or bone age advancement. The higher dose was in general not associated with an increased incidence of adverse events, confirming the known tolerability of higher GH and IGF-I levels in adolescents. Laboratory parameters including measures of glucose metabolism and antibodies to GH were likewise unaffected by the higher dose.

Genentech intends to file a safety update to this submission approximately four months after this submission, which should contain complete and final safety data for the study.

Two paper copies of this submission have been sent to the Agency, jacketed as clinical, and statistical review copies. A CD-ROM (
containing the entire archival copy of the submission and relevant SAS datasets is also provided. Case Report Tabulations and Case Report Forms are submitted electronically only. This CD has been checked for computer viruses using Norton AntiVirus for Windows NT Workstation (with virus definitions dated 4/22/99), and is hereby certified to be virus-free.

We have enclosed a revised package insert for Nutropin® [somatropin (rDNA origin) injection] with our proposed changes added. The additions are indicated by underlined text, and include annotated references.

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

19676-093 sub ss

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

IND [redacted]

9029

RECEIVED

AUG 15 1994

REGULATORY AFFAIRS

AUG 9 1994

Genentech, Inc.
Attention: M. David MacFarlane, Ph.D.
Vice President, Regulatory Affairs
460 Point San Bruno Boulevard
South San Francisco, CA 94080

Dear Dr. MacFarlane:

Please refer to your Investigational New Drug Application (IND) for Nutropin [somatropin (rDNA origin) for injection], IND [redacted]

We also refer to your communication dated September 22, 1992, requesting input from the Division regarding the necessity of two clinical trials to support a new dosing regimen for growth hormone in pubertal children.

We further refer to your annual report dated April 20, 1994, which included, among other things, the same request (specifically, a request that you be provided, in writing, confirmation of the telephone conversation between Dr. Ursala Fritsch, of your office, and Ms. Lana Braithwaite (now Pauls) of this Division on August 17,1992, in which she indicated that only one clinical trial would be required.

We have completed our review of these submissions and have the following comments:

> The single study, identified as M0380g, will be sufficient to support a new dosing regimen in pubertal children.

Should you have any questions, please contact Ms. Lana Pauls at (301) 443-3510.

Your cooperation is appreciated.

Sincerely yours,

/S/

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

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on last page.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Genentech, Inc.	June 11, 1999
TELEPHONE NO. *(Include Area Code)*	**FACSIMILE (FAX) Number** *(Include Area Code)*
(650) 225-1202	(650) 225-1397

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):*
1 DNA Way
South San Francisco, California, USA 94080-4990
License 1048

AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE*

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (if previously issued) NDA 19-676

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY	
somatropin (rDNA origin) for injection	Nutropin®	
CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)*		**CODE NAME** *(if any)*
recombinant human growth hormone		
DOSAGE FORM:	**STRENGTHS:**	**ROUTE OF ADMINISTRATION:**
lyophilized	5mg vial,10mg vial	subcutaneous injection

(PROPOSED) INDICATION(S) FOR USE:
growth failure due to a lack of endogenous growth hormone

APPLICATION INFORMATION

APPLICATION TYPE (check one) ■ NEW DRUG APPLICATION (21 CFR 314.50) □ ABBREVIATED APPLICATION (ANDA, AADA, 21CFR 314.94) □ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ■ 505 (b) (1) □ 505 (b) (2) □ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one)
□ ORIGINAL APPLICATION □ AMENDMENT TO A PENDING APPLICATION □ RESUBMISSION
□ PRESUBMISSION □ ANNUAL REPORT □ ESTABLISHMENT DESCRIPTION SUPPLEMENT □ SUPAC SUPPLEMENT
□ EFFICACY SUPPLEMENT ■ LABELING SUPPLEMENT □ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT □ OTHER

REASON FOR SUBMISSION
To add additional pubertal dose to label

PROPOSED MARKETING STATUS (check one) ■ PRESCRIPTION PRODUCT (Rx) □ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 8 — THIS APPLICATION IS □ PAPER ■ PAPER AND ELECTRONIC □ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

GENENTECH, INC.
1 DNA WAY
SOUTH SAN FRANCISCO, CALIFORNIA 94080-4990

s References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs refer referenced in the current .cation)

NDA 20-522, IND

	This application contains the following items: *(Check all that apply)*
X	1. Index **paper/electronic**
X	2. Labeling (check one) ☒ Draft Labeling ☐ Final Printed Labeling **paper/electronic**
	3. Summary (21 CFR 314.50 (c))
	4. Chemistry Section
	A. Chemistry, manufacturing, and controls information (e.g. 21 CFR 314.50 (d) (1), 21 CFR 601.2)
	B. Samples (21 CFR 314.50 (e) (1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
	C. Methods validation package (e.g. 21 CFR 314.50 (e) (2) (i), 21 CFR 601.2)
	5. Nonclinical pharmacology and toxicology section (e.g. 21 CFR 314.50 (d) (2), 21 CFR 601.2)
	6. Human pharmacokinetics and bioavailability section (e.g. 21 CFR 314.50 (d) (3), 21 CFR 601.2)
	7. Clinical Microbiology (e.g. 21 CFR 314.50 (d) (4))
X	8. Clinical data section (e.g. 21 CFR 314.50 (d) (5), 21 CFR 601.2) **paper/electronic**
	9. Safety update report (e.g. 21 CFR 314.50 (d) (5) (vi) (b), 21 CFR 601.2)
	10. Statistical section (e.g. 21 CFR 314.50 (d) (6), 21 CFR 601.2)
X	11. Case report tabulations (e.g. 21 CFR 314.50 (f) (1), 21 CFR 601.2) **electronic**
X	12. Case reports forms (e.g. 21 CFR 314.50 (f) (2), 21 CFR 601.2) **electronic**
	13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A))
	15. Establishment description (21 CFR Part 600, if applicable)
X	16. Debarment certification (FD&C Act 306 (k) (1)) **paper/electronic**
	17. Field copy certification (21 CFR 314.5 (k) (3))
X	18. User Fee Cover Sheet (Form FDA 3397) **paper/electronic**
X	19. OTHER (Specify) **Disclosure of financial interests of clinical investigators (paper/electronic)**

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211, 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR 202.
5. Regulations on making changes in application in 21 CFR 314.70, 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on reports in 21 CFR 314.80,314.81, 600.80 and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: a willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
	Robert L. Garnick, Ph.D., Vice President, Regulatory Affairs	**June 11, 1999**

ADDRESS *(Street, City, State, and ZIP code)*	Telephone Number
1 DNA Way, South San Francisco, CA 94080-4990	**(650) 225-1202**

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-676/S-016

JUN 28 1999

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

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

Dear Dr. Garnick:

We acknowledge receipt of your supplemental application for the following:

Name of Drug:	Nutropin® [Somatropin (rDNA origin) for Injection]
NDA Number:	19-676
Supplement Number:	S-016
Date of Supplement:	June 11, 1999
Date of Receipt:	June 14, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on August 13, 1999, 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
Rockville, MD 20857

Sincerely,

/S/

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine
Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:

cc:
Original NDA 19-676/S-016
HFD-510/Div. Files
HFD-510/CSO/C. King

filename: C:\WPFILES\19676ACK.WPD

SUPPLEMENT ACKNOWLEDGEMENT