2) If the answer to 2 b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?	Yes		No	✓
If yes, explain:				
c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:				
Investigation #1, Study #: M038lg	IND [redacted]			
Investigation #2, Study #:				
Investigation #3, Study #:				
3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.				
a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")				
Investigation #1	Yes		No	✓
Investigation #2	Yes		No	
Investigation #3	Yes		No	
If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?				
Investigation #1	Yes		No	✓
Investigation #2	Yes		No	
Investigation #3	Yes		No	
If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):				
Investigation #1 M038lg - updated information				

Investigation #2				
Investigation #3				

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 M038[illegible]	Yes	✓	No	
IND#:				
Explain:				
Investigation #2	Yes		No	
IND#:				
Explain:				
Investigation #3	Yes		No	
IND#:				
Explain:				

b. For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	Yes		No	
IND#:				
Explain:				
Investigation #2	Yes		No	
IND#:				
Explain:				
Investigation #3	Yes		No	
IND#:				
Explain:				

c. Notwithstanding an answer of "yes" to (a) or (b), are there

other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)	Yes		No	✓
If yes, explain:				

BACK TO TOP

/S/

Signature of PM/CSO

Date: 11/16/99

APPEARS THIS WAY
ON ORIGINAL

Signature of Division Director

Date: 11/30/99

/S/

cc: 19-676

Original NDA

Division File

HFD-93 Mary Ann Holovac

BACK TO TOP

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

~~BLA~~ # 19-676 Supplement # 013 Circle one (SE1) SE2 SE3 SE4 SE5 SE6 (SE8)

Nutropin (somatropin [rDNA origin])

HFD 510 Trade and generic names/dosage form: for injection) Action (AP) AE NA

Applicant Genentech Therapeutic Class growth hormones

Indication(s) previously approved Pediatric patients: (1) long-term tx of growth failure due to lack of adequate endogenous GH secretion; (2) tx of growth failure associated w/chronic renal insufficiency; (3) tx of short stature for Turner Syndrome. Adult patients: replacement of endogenous GH who meet specified criteria

Pediatric information in labeling of approved indication(s) is adequate ✓ inadequate ___

Proposed indication in this application no change

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___Yes (Continue with questions) ✓ No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

___Neonates (Birth-1month) ___Infants (1month-2yrs) ___Children (2-12yrs) ___Adolecents(12-16yrs)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.

- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

___ 5. **If none of the above apply,** attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___ Yes ✓ No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from medical team leader (e.g., medical review, medical officer, team leader)

/S/ 11/5/99

Signature of Preparer and Title Date

Orig NDA/~~BLA~~ # 19-676-S013
HFD-510 /Div File
NDA/~~BLA~~ Action Package
HFD-006/ KRoberts

(revised 10/20/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

16. DEBARMENT CERTIFICATION

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

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

Signed by: Robert L Gh

Robert L. Garnick, Ph.D

Title: Vice President, Regulatory Affairs

Date: 11/5/99

Date: November 1, 1999 /S/

From: Saul Malozowski
Medical Officer

Subject: NDA 19-676 SE1-013, Nutropin changes in bone mineral density; Biopharm review

To: The file

This NDA supplement was an extension of the original studies that composed this NDA. The original NDA review covered all relevant biopharmaceutical issues. Thus, it was determined that a biopharm review was not required for this supplement.

APPEARS THIS WAY
ON ORIGINAL

Division of Metabolic and Endocrine Drug Products, HFD-510

Review of Draft Labeling

Application Number: 19-676/S-013

Name of Drug: Nutropin® (somatropin [rDNA origin] for injection)

Sponsor: Genentech, Inc.

Material Reviewed

Submission Date: November 5, 1999

Receipt Date: November 8, 1999

Review

The draft labeling submitted on November 5, 1999 has been reviewed. This labeling has been compared to the FPL submitted on April 30, 1999, as (Supplement-015), approved by the Agency on November 24, 1999. The changes to the draft labeling for S-013 are as follows:

1. Page 14. In the **CLIN PHARM** section, under the subsection **Adult Growth Hormone Deficiency (GHD)**, there is an additional paragraph regarding an increase in spine bone mineral density.

2. Page 4. In the **CLIN PHAM** section, under the **Mineral Metabolism** subsection, there is an additional statement regarding increases in serum alkaline phosphatase.

The above changes are highlighted and attached to this review and are acceptable.

/S/ 11/24/99
Dwayne Keels

/S/ 11/24/99
Crystal King, P.D., M.G.A.

/S/ 11/29/99
Enid Galliers, CPMS

/S/ 11/30/99
Saul Malozowski, M.D.

/S/ 11/30/99
Joy Mele, Statistician

/S/ 11/30/99
Todd Sahlroot, Statistical TL

cc:
HFD-510/DivFile
HFD-510/Keels

RECORD OF TELEPHONE CONVERSATION/MEETING	Date: November 1, 1999
At 12:00 noon, EST, I left a voice message for Shawn requesting that a NEW final draft label amendment be submitted. The final draft label submitted on 10/29/99 contained two errors to be corrected to: (1) (2) in Contraindications: Further, I requested that the debarment statement and patent information and statement be submitted. /S/ 11/1/99 **Crystal King, P.D., M.G.A.,** **Regulatory Project Manager**	**NDA#: 19-676-013** **20-522-009** **Telecon/Meeting initiated by:** ○ Applicant/Sponsor ● FDA **By:** Telephone **Product Name:** Nutropin **Firm Name:** Genentech **Name and Title of Person with whom conversation was held:** Shawn McLaughlin **Phone:** 650-225-1915

cc: NDA 19-676
NDA 20-522
Div Files

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

1 DNA Way
South San Francisco, CA 94080-4990 USA
Phone: (650) 225-2631
Fax: (650) 225-3117
E-mail: kma@gene.com

October 12, 1999

Saul Malozowski, MD, PhD, Medical Team Leader
Division of Metabolic and Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research, Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Subject: Nutropin NDA 19-676, S-013, Bone Mineral Density Label

Dear Dr. Malozowski:

Please see the attached revised PI proposal based on our discussion today. You can respond via FAX to the regulatory department at 650-225-1397. Thank you for your careful consideration of this.

Sincerely,

Ken Attie

Kenneth M. Attie, MD
Sr. Clinical Scientist, Genentech, Inc

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

1 DNA Way
South San Francisco, CA 94080-4990 USA
Phone: (650) 225-2631
Fax: (650) 225-3117
E-mail: kma@gene.com

October 8, 1999

Saul Malozowski, MD, PhD, Medical Team Leader
Division of Metabolic and Endocrine Drug Products, HFD-510
Center for Drug Evaluation and Research, Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Subject: Nutropin NDA 19-676, S-013, Bone Mineral Density Label

Dear Dr. Malozowski:

Thank you for sending to us the proposed wording for the BMD data to be added to the adult GHD section of the Nutropin label. Please see the attached proposal we have come up with after some internal discussions. We have performed some statistical calculations where you had blanks for data. In general, the p-values are derived from Wilcoxon sign rank (within group) and rank sum (between groups) tests. We have tried to include all of the major points you want to make, while revising the wording to add clarification. Please send your comments to me directly via FAX at 650-225-3117 (work) or 415-664-4494 (home). Feel free also to call at home at 415-664-4550.

Sincerely.

Ken Attie

Kenneth M. Attie, MD
Sr. Clinical Scientist, Genentech, Inc

Genentech, Inc.

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

NDA SUPP AMEND
SES-013
BL

May 14, 1999

CENTER FOR DRUG
REC'D
MAY 17 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-013
Nutropin® [somatropin (rDNA origin) for injection]
Adult Growth Hormone Deficiency
Supplement: Additional Label Claim
Bone Mineral Density
Amended Revision to Package Insert

Dear Dr. Sobel:

REVIEWS COMPLETED
CSO
DATE

Reference is made to our Supplemental New Drug Application, NDA 19-676, S-013, for Nutropin® [somatropin (rDNA origin) for injection], submitted January 29, 1999, providing clinical data to support an additional label claim of improved bone mineral density (BMD) with Nutropin treatment in adults with growth hormone deficiency. This submission contains a revised package insert (PI) that supersedes the previous version provided in the January 29, 1999 supplement.

As was mentioned in our teleconference with Dr. Malozowski and Ms. Crystal King on April 27, 1999, we feel that the addition of a figure to the PI could be very helpful to prescribers with respect to the time course and pattern of change for BMD. In particular, Figure 7, "Percent Change from Baseline in DEXA Spine BMD for Subjects in Study M0381g with baseline and 24-Month

Data," from the submission would complement the text that we have already proposed to be added to the label.

Enclosed is a revised package insert for Nutropin that incorporates the figure, as well as the following additional statement in the Mineral Metabolism section of CLINICAL PHARMACOLOGY:

[redacted]

The proposed additions are shown as underlined text in the annotated version of the package insert.

Additionally, the updated package insert for Nutropin reflects two other changes; one regarding safety information specifically requested by FDA in a letter to growth hormone manufacturers dated January 4, 1999, and one to comply with requirements under 21 CFR 201.57(f)(10)(ii)(A), for the addition of a "Geriatric Use" statement. Final Printed Labeling for Nutropin, updated with these changes, was submitted to the Agency as a Special Supplement, Changes Being Effected on April 30, 1999 (NDA 19-676).

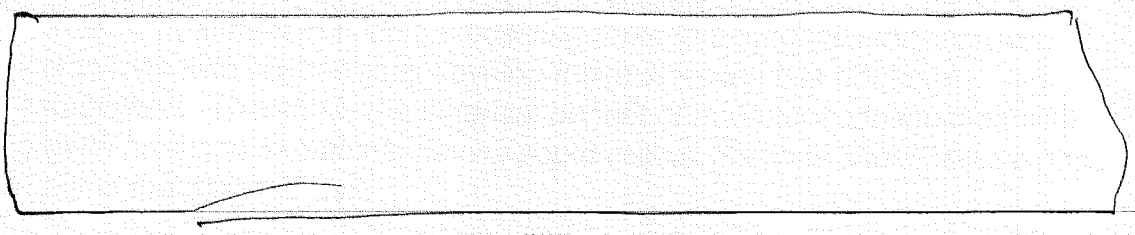
These changes are as follows:

CONTRAINDICATIONS

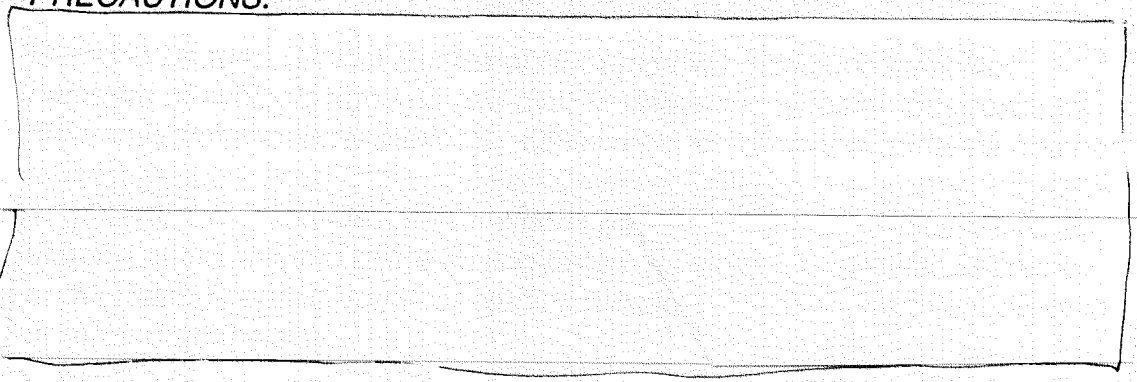
[redacted]

WARNINGS

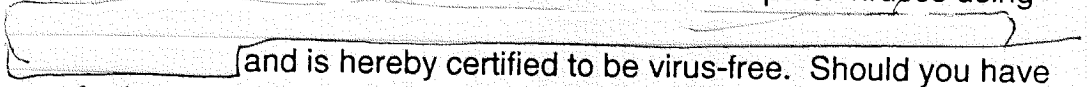
[redacted]



PRECAUTIONS:



The enclosed CD-ROM contains a revised annotated and clean version of the Nutropin PI. This CD has been checked for computer viruses using



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

ORIGINAL

Genentech, Inc.

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

NDA NO. 19-676 REF NO. 013
NDA SUPPL FOR S61

January 29, 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

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ M.
ELS

Subject: **NDA 19-676**
Nutropin® [somatropin (rDNA origin) for injection]
Supplement - Additional Label Claim
Bone Mineral Density

Dear Dr. Sobel:

Reference is made to our Supplemental New Drug Application, NDA 19-676, S-009, for Nutropin® [somatropin (rDNA origin) for injection], approved on December 15, 1997 for replacement of endogenous growth hormone (GH) in adults with GH deficiency (AGHD). This submission provides a clinical data supplement to support an additional label claim for improved bone mineral density (BMD) with Nutropin treatment in the adult patient population.

Genentech's product labeling for Nutropin currently contains a discussion of body composition, lipid metabolism, and other data from the pivotal trials in adults intended to assist physicians in understanding the expected effects of therapy. However, the PI lacks information regarding the effects of replacement therapy with GH on bone density in part because relevant data analysis was not available at the time of the original NDA supplemental submission (NDA 19-676, S-009, 13 December 1996). New data contained in this submission indicate that statistically and clinically significant changes in spine BMD were observed with

19676-083 sub ss

This submission contains no preclinical data and the labeling change is not under the purview of Pharmacology; thus, we would have no objection to Filing of this labeling change supplement. No review necessary.
/S/
11 Mar 99

24 months of therapy in Study M0381g at doses of 0.0125 mg/kg and 0.025 mg/kg. As this is an important endpoint of therapy for potential adult patients with childhood-onset GHD, it is appropriate to add a well-balanced statement regarding the effects of treatment observed in the study to the labeling.

Three copies of this submission have been sent to the Agency, jacketed as archival, clinical, and statistical review copies. A CD-ROM containing the entire submission and relevant SAS datasets for use as a reviewer's aid is also provided. This CD has been checked for computer viruses using Network Associates VirusScan NT (using virus definitions 3.0.3111), and is hereby certified to be virus-free.

We have enclosed a revised package insert for Nutropin® [somatropin (rDNA origin) for injection] with the bone mineral density claim added. The addition is indicated by underlined text.

Since the adult GHD indication has orphan drug designation (application #96-1003), and since this BMD label claim relates only to that indication, we intend to apply for a refund of the application fee paid in connection with this supplement.

Should you have any questions regarding this submission please contact Ms. Fiona Cameron of my staff at (650) 225-1818.

Sincerely,

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

19676-083 sub ss

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-676/S-013

FEB 17 1999

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

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-013
Date of Supplement:	January 29, 1999
Date of Receipt:	February 1, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on April 2, 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

NDA SUPP AMEND
SE8-013- BL

Genentech, Inc.

ORIGINAL

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

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

October 29, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D 10/29/99
OCT 28 1999
HFD-510

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-013**
Nutropin® [somatropin (rDNA origin) for injection]
Adult Growth Hormone Deficiency
Supplement: Additional Label Claim
Bone Mineral Density
Final Draft Labeling

Dear Dr. Sobel:

Reference is made to our Supplemental New Drug Application, NDA 19-676, S-013 for Nutropin® [somatropin (rDNA origin) for injection], providing clinical data to support an additional label claim of improved bone mineral density (BMD) in adults with growth hormone deficiency. Specifically, we refer to the draft package insert (PI). The first draft PI was submitted with the original supplement on January 29,1999, and subsequently amended on May 14, 1999. Additional facsimile communications dated October 8, 12, 27, and 28 were also part of labeling discussions.

With the October 28 communication it appears that all labeling issues have been addressed. The enclosed CD-ROM contains an annotated and clean version of the final draft Nutropin PI, as well as copies of all facsimile communications between Genentech and the Agency involving finalization of the labeling. This