CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-280/S-031

CORRESPONDENCE

* Similar Py commitment for Periatric Safety Report Update section for a new indication/dose.

NDA 19-676/S-016

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

Dear Dr. Garnick:

Please refer to your supplemental new drug application dated June 11, 1999, received June 14, 1999, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Nutropin (somatropin [rDNA origin] for injection).

We acknowledge receipt of your submissions dated August 5 and November 19, 1999, and March 27 and 30, and April 11, 2000.

This supplemental new drug application provides for the addition of a higher dose of Nutropin (somatropin [rDNA origin] for injection) for pubertal patients (pubertal dose $\leq$ 0.7 mg/kg/wk) to the **DOSAGE AND ADMINISTRATION** section of the product insert.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

You are not required to complete a pediatric assessment for this application because it is not covered by the Pediatric Rule (21 CFR 314.55(a)).

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted April 11, 2000).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 19-676/S-016." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitments specified in your submission dated March 30, 2000. These commitments, along with any completion dates agreed upon, are listed below.

Genentech will provide the following updates for the four-year period following the commercial launch of the pubertal dose regimen:

1. NDA Annual Reports – You will create a subsection of the National Comparative Growth Study update section and use this to report the number of patients receiving a dose greater than or equal to 0.4 mg/kg/week. Further, you will discuss any other information available relevant to these patients.

2. Periodic Safety Reports – You will create a section that describes the spontaneous adverse event reports and the safety information from National Comparative Growth Study for patients receiving greater than or equal to 0.4 mg/kg/week dosing. This section will discuss the safety profile of these patients as compared to patients receiving doses of less than 0.4 mg/kg/week (excluding Turner Syndrome and Chronic Renal Insufficiency patients).

3. Expedited Adverse Event Reports – For any relevant expedited adverse event reports, at the beginning of the narrative in section B-5, "Describe Event or Problem," of the Med Watch Form 3500A, you will use surrounding asterisks to emphasize that the patient was being dosed at greater than or equal to 0.4 mg/kg/week. You will also include this information in the cover letter that accompanies each of these reports, again highlighted in such a manner as to draw immediate attention to the fact.

Data and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

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

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

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

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

Sincerely yours,

John K. Jenkins, M.D.
Acting Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of Orphan Products Development *(HF-35)*
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

June 29, 2000

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, Michigan 49001

Attention: Cynthia Blanchard
Regulatory Affairs

Dear Ms. Blanchard:

Reference is made to the orphan drug application of March 30, 2000 submitted pursuant to Section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb) for the designation of somatropin as an orphan drug (application #00-1354).

We have completed the review of your application and have determined that somatropin does not qualify for orphan drug designation for use in the long-term treatment of growth failure in children who were born small for gestational age (SGA). The goal in treating growth failure in children born SGA is to normalize childhood growth and final stature. While using somatropin to induce pre-pubertal catch-up growth in SGA children should help achieve these goals, you indicate that continued pharmacological GH therapy during puberty should enhance growth as well, further contributing to a positive outcome. However, you do not account for the use of somatropin during puberty in your prevalence estimate and adding pubertal children to this indication would exceed the population threshold for orphan drug designation.

Further review of this application is being held in abeyance pending receipt of any new information. A written response to this letter must be received within 90 days from the date of this communication or the file will be considered inactive and withdrawn. Following 90 days, further requests for designation of the same product for the same indication must be made in the form of a new designation application. Information contained in this file may be cross-referenced in support of a new designation request.

Please provide copies of appropriate references used in support of any new submissions. Your cooperation is appreciated.

Sincerely yours,

Marlene E. Haffner, MD, MPH
Rear Admiral, United States Public Health Service
Director, Office of Orphan Products Development

DUPLICATE

NDA NO. 20-280 REF. NO. 051
NDA SUPPL FOR SE1

Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-8668

CENTER FOR DRUG EVALUATION AND RESEARCH
RECEIVED
JUL - 3 2000
HFD-510

June 30, 2000

Division of Metabolism and Endocrine Drug Products HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
Attn: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-280
GENOTROPIN®
(somatropin [rDNA origin] for injection)

SUPPLEMENT
Treatment of Growth Failure in Children Born Small for Gestational Age

Dear Sir or Madam:

Under the provisions of 21CFR 314.71, Pharmacia & Upjohn is submitting an efficacy supplement to NDA 20-280, GENOTROPIN (somatropin [rDNA origin] for injection), to provide for long-term treatment of growth failure in children born small for gestational age (SGA).

Clinical Information
The clinical information provided in this supplement includes data from four controlled trials performed in France (TRN 89-041), the Nordic countries (TRN 89-070-017), Germany, (TRN 90-079, and Belgium (TRN 90-080/98-8122-011). The studies were of similar design, being open-label multi-center studies where patients were randomized into three parallel groups. Two of the groups were devoted to active treatment in different dosages, and the third group served as an untreated control. In a meeting with the Agency on November 10, 1999, agreement was made that catch-up growth, as demonstrated in these four studies, is acceptable to use as the primary efficacy variable in our sNDA for the use of GENOTROPIN in the treatment of growth failure in children born SGA.

User Fee
An application for Orphan Drug Designation was submitted March 30, 2000 to FDA Division of Orphan Drug Products for the SGA indication. Because our Orphan Drug application is still under review, a User Fee check made payable to the Food and Drug Administration in the amount [redacted] If Orphan Drug Designation is eventually granted, we plan to request a waiver of the User Fee for this application.

Application format
An abbreviated Table of Contents for this application is provided on the following page. The more detailed Overall Index for this application is located in Volume 1. The first volume of each item contains a comprehensive table of contents for that item. Each volume within the item is also prefaced with a table of contents specific to that volume.

The volumes are sequentially numbered within each item. Each volume also bears an overall volume number on the binder cover. The overall volume numbers are *not* used for cross-referencing.

Submission information
Data are being provided in print or electronic format, as described below and on the abbreviated Table of Contents on the following page.

- Paper submission: archival and review copies of all volumes for Items 1, 2, 3, and 8/10. Two review copies of Item 8/10 are provided for the Clinical and Statistical reviews, respectively.

- Electronic submission: archival and review copies of Item 11 (Case Report Tabulations - CRT) and Item 12 (Case Report Forms - CRF) are being submitted on one CD-ROM in electronic form only. In addition, copies of this letter (*cover.pdf*), a signed Form 356h (*356h.pdf*), the abbreviated Table of Contents (*ndatoc.pdf*), and a Word version of the proposed labeling are included on the CD-ROM. The CD-ROM, located in Volume 1, has been scanned with Network Associate's McAfee Virus Scan for Windows version 4.0.3 and was found to be virus free. One archival and one review copy of the CD-ROM are included in this submission.

If you have any questions regarding the content of this submission, please contact me by telephone at (616) 833-6717 or fax at (616) 833-8237.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Cynthia J. Blanchard
Regulatory Manager

CJB:mlw

king

NDA 20-280/S-031

PRIOR APPROVAL SUPPLEMENT

Pharmacia & Upjohn Company
Attention: Cynthia J. Blanchard
Regulatory Manager
7000 Portage Road
Kalamazoo, Michigan 49001

JUL 19 2000

Dear Ms. Blanchard:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Genotropin (somatropin [rDNA origin] for injection)
NDA Number:	20-280
Supplement Number:	S-031
Therapeutic Classification:	Priority (P)
Date of Supplement:	June 30, 2000
Date of Receipt:	July 3, 2000

This supplement proposes a new indication, for Genotropin, to provide for long-term treatment of growth failure in children born small for gestational age (SGA).

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on September 1, 2000, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be January 3, 2001.

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

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

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

U.S. Postal Service/Courier/Overnight Mail:

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

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

Sincerely,

/S/

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

DUPLICATE

Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

SF 1 | BM 031

July 31, 2000

Dr. Robert Perlstein
Division of Metabolism and Endocrine Drug Products HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-280/S-031
GENOTROPIN®
(somatropin [rDNA origin] for injection)

AMENDMENT
Initial European Application for SGA

Dear Dr. Perlstein:

We refer to your request received by telephone July 21, 2000, for a signed statement regarding reasons for refusal of the initial European application for use of GENOTROPIN in children born small for gestational age (SGA). In response to your request, we have enclosed a copy of a signed letter from Professor Rolf Bass that communicates the reasons for refusal of the initial SGA application in Europe.

A chronology of the steps of the initial European application is summarized below. Documentation of these steps is found in the attached letter from [redacted]

1. The initial application (Type II Variation) was submitted in February 1996.
2. The Concerned Member States were not able to reach agreement in respect to approval of the variation.
3. The application was referred to the Committee for Proprietary Medicinal Products (CPMP) for arbitration on June 19, 1996. Eight points to be considered by the CPMP were drawn from the comments from Concerned Member States.
4. Pharmacia & Upjohn (P&U) provided written responses to these questions on September 1, 1996.
5. After assessment of P&U's responses, the CPMP concluded that the variation should not be approved [redacted]

The Grounds for Refusal as stated in Annex B of the attached letter from [redacted] reads as follows:

"Whereas, the studies failed to demonstrate the clinical benefit in the indication applied for:

- *as there was a lack of data on final height*
- *as the data provided were insufficient to anticipate the treatment effect on final height*
- *as there were no controlled trials demonstrating psycho-social benefits*

Whereas,

- *the data submitted have not adequately addressed possible loss of final height attributable to apparent progression in bone maturation*

The [redacted] recommends the refusal of the variation applied for."

Please note that P&U is actively pursuing plans to resubmit the SGA application in Europe in the near future.

If you have any questions regarding this information, please contact me by telephone at (616) 833-6717 or by fax at (616) 833-8237.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Cynthia J Blanchard

Cynthia J. Blanchard
Regulatory Manager

CJB:lmf
Attachment
cc: Crystal King, Project Manager

Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone (616) 833-4000

August 9, 2000

Division of Metabolism and Endocrine Drug Products HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-280/S-031
GENOTROPIN™
(somatropin [rDNA origin] for injection)

AMENDMENT
Provocation Test Code List

Dear Sir/Madam:

Please refer to NDA 20-280/S031 submitted June 30, 2000, for the use of GENOTROPIN in the treatment of growth failure in children born small for gestational age. In a telephone conversation between Cynthia Blanchard (Pharmacia & Upjohn) and Crystal King, Division of Metabolism and Endocrine Drug Products, on August 4, 2000, a request was made on behalf of statistician Dr. James Gebert for information to decode the numbers listed in the Case Report Tabulations of Study 89-041, Table GHDEF, under the column entitled "Test Drug."

The numeric codes refer to which provocation test was used to confirm or reject the diagnosis of growth hormone deficiency. A list of the codes and associated provocation tests is provided as an attachment to this letter.

If you have any questions regarding this information, please contact me by telephone at (616) 833-6717 or by fax at (616) 833-8237.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Cynthia J. Blanchard

Cynthia J. Blanchard
Regulatory Manager

CJB:kmv

DUPLICATE

SE1/031
NC

Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone (616) 833-4000

September 6, 2000

Division of Metabolism and Endocrine Drug Products HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-280/S-031
GENOTROPIN®
(somatropin [rDNA origin] for injection)

AMENDMENT
Requested Information

Dear Sir or Madam:

We refer to a request received by telephone August 31, 2000, from Dr. Robert Perlstein, Medical Reviewer, for a listing of investigator sites, numbers of patients, study monitors for study, comments from study monitors, and information regarding central locations for clinical documentation. The requested information is provided as attachments to this letter, as follows:

Attachment 1 - List of Investigators/Monitors Belgian Protocol 90-080/98-8122-011
Attachment 2 - List of Investigators/Monitors German Protocol CTN 90-079
Attachment 3 - List of Investigators/Monitors Nordic Protocol 89/070-071
Attachment 4 - List of Investigators/Monitors French Protocol 89/041
Attachment 5 - Clinical Document Storage

We also refer to comments received by telephone August 31, 2000, from Ms. Crystal King, Project Manager, on behalf of Dr. James Gebert, Statistical Reviewer. Dr. Gebert's comments are listed below in **bold** with our answers following. These observations will be corrected in the amended documents to be submitted by September 29, 2000.

1. **Item 8/10, Volume 23, Page 41, Table.**
   The table contains 12-24 month p-values. The text under the table starting with the sentence "During the 2nd year..." contains p-values that do not match those in the table.

   The figures in the table are correct. The numbers in the text are incorrect.

2. **Item 8/10, Volume 20, Page 37.**
   The order of the months in the 0-12 month data is mixed up.

   The correct figures are as follows:

	Month 0-12	
	N	Mean (SD)
0.033	16	2.4 (1.4)
0.067	18	4.0 (1.5)
Untreated	11	-1.2 (0.9)

If there are any questions regarding this submission, please contact me by telephone at (616) 833-6717 or by fax at (616) 833-8237.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Cynthia J. Blanchard

Cynthia J. Blanchard
Regulatory Manager

CJB:lmf

Attachments

DUPLICATE

NEW CORRESP

Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

September 7, 2000

Division of Metabolism and Endocrine Drug Products HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-280/S-031
GENOTROPIN®
(somatropin [rDNA origin] for injection)

AMENDMENT
Letter from Office of Orphan Products Development

Dear Sir or Madam:

Reference is made to a request received by telephone August 31, 2000, from Ms. Crystal King for a copy of the letter received from the Office of Orphan Products Development in response to our orphan drug application of March 30, 2000. The orphan application (#00-1354) was for use of GENOTROPIN in the long-term treatment of growth failure in children who were born small for gestational age (SGA).

Attached is a copy of the requested letter.

If there are any questions regarding this submission, please contact me by telephone at (616) 833-6717 or by fax at (616) 833-8237.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Cynthia J. Blanchard

Cynthia J. Blanchard
Regulatory Manager

CJB:lmf

Attachments

DUPLICATE

SE 1-031
BM

Pharmacia&Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

September 11, 2000

Division of Metabolism and Endocrine Drug Products HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-280/S-031
GENOTROPIN®
(somatropin [rDNA origin] for injection)

AMENDMENT
Updated Table (Clinical Document Storage)

Dear Sir or Madam:

We refer to an amendment to NDA 20-280/S-031 submitted September 6, 2000. An updated version of Attachment 5 (Clinical Document Storage) of that submission is attached to this letter. This updated table was also provided by fax on September 8, 2000.

If there are any questions regarding this submission, please contact me by telephone at (616) 833-6717 or by fax at (616) 833-8237.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Cynthia J. Blanchard

Cynthia J. Blanchard
Regulatory Manager

CJB:lmf

Attachments

NDA SUPP AMEND
8-31-00

Pharmacia&Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

September 15, 2000

Division of Metabolism and Endocrine Drug Products HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-280/S-031
GENOTROPIN®
(somatropin [rDNA origin] for injection)

AMENDMENT
Responses to Requests from Teleconference
Sept. 1, 2000

Dear Sir or Madam:

Reference is made to requests received during a teleconference September 1, 2000, between Drs. Robert Perlstein and James Gebert, FDA Medical and Statistical Reviewers, respectively, and Pharmacia & Upjohn (P&U). Participants from P&U were as follows: Kalamazoo, MI - Cynthia Blanchard, Michael Burdick, Dan Chirby (Regulatory Affairs); Peapack, NJ - Myrlene Staten, M.D. (Clinical Development); Stockholm, SWE - Birgitta Lange-Sjöblom (Clinical Development), Lisa Andersson, Don Gieseker (Regulatory Affairs), Henrik Franzon, John Schoenfelder (Statistics), Ulf Stenberg (Project Management).

Requests made by Dr. Perlstein were as follows:

1. Construction of one table per efficacy variable (including primary as well as secondary variables) to include data from each study for side by side comparison.
2. New presentation of supportive data from study years 2-6, presented per study and including how many patients stayed caught up *vs.* how many had to be restarted on the GH therapy.
3. Translation of SDS measurements to quantifiable changes in cm. or cm./year.
4. Justification of our use of parental adjusted height rather than predicted adult height as an efficacy measurement.
5. P&U response to the [redacted] questions that were supplied as an amendment to the application on July 31, 2000.

Our responses to these requests are included in the attached documentation. This information will be provided to Dr. Perlstein as a desk copy on CD-ROM within the next few days.

If there are questions regarding this information, please contact me by telephone at (616) 833-6717 or by fax at (616) 833-8237.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Cynthia J. Blanchard

Cynthia J. Blanchard
Regulatory Manager

CJB:lmf

Attachments

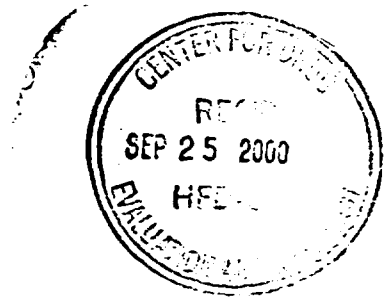
DUPLICATE

SE1/031
C

Pharmacia&Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

September 22, 2000



Division of Metabolism and Endocrine Drug Products HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-280/S-031
GENOTROPIN®
(somatropin [rDNA origin] for injection)

Amendment to Supplement
Precocious Puberty

Dear Sir or Madam:

We refer to a request received from Saul Malozowski, M.D., in a telephone conversation with Barbara Lippe, M.D. (Pharmacia & Upjohn) on August 15, 2000, for information regarding precocious puberty, as follows:

1. Literature or information on the incidence of sexual precocity in SGA (with and without GH treatment)
2. Literature or a description of what the normal range of sexual maturation tends to be in these children
3. Whether there is sexual precocity reported in SGA children in KIGS
4. Whether there is sexual precocity reported in GHD children in KIGS and, if so, incidence numbers.

Our responses to these requests are included in the attached documentation.

If there are questions regarding this information, please contact me by telephone at (616) 833-6717 or by fax at (616) 833-8237.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Cynthia J. Blanchard

Cynthia J. Blanchard
Regulatory Manager

CJB:SEH
Attachments

Pharmacia&Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

September 21, 2000

Division of Metabolism and Endocrine Drug Products HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-280/S-031
GENOTROPIN®
(somatropin [rDNA origin] for injection)

ATTN: CRYSTAL KING - DESK COPIES

Dear Crystal:

Reference is made to requests received during a teleconference September 1, 2000, between Drs. Robert Perlstein and James Gebert (FDA Medical and Statistical Reviewers, respectively, and Pharmacia & Upjohn (P&U). Participants from P&U were as follows: Kalamazoo, MI - Cynthia Blanchard, Michael Burdick, Dan Chirby (Regulatory Affairs); Peapack, NJ - Myrlene Staten, M.D. (Clinical Development); Stockholm, SWE - Birgitta Lange-Sjöblom (Clinical Development), Lisa Andersson, Don Gieseker (Regulatory Affairs), Henrik Franzon, John Schoenfelder (Statistics), Ulf Stenberg (Project Management).

Requests made by Dr. Perlstein were as follows:

1. Construction of one table per efficacy variable (including primary as well as secondary variables) to include data from each study for side by side comparison.
2. New presentation of supportive data from study years 2-6, presented per study and including how many patients stayed caught up *vs.* how many had to be restarted on the GH therapy.
3. Translation of SDS measurements to quantifiable changes in cm. or cm./year.
4. Justification of our use of parental adjusted height rather than predicted adult height as an efficacy measurement.
5. P&U response to the [redacted] questions that were supplied as an amendment to the application on July 31, 2000.

On September 15, 2000, we sent a paper submission containing responses to these requests to FDA. The three CD-ROMs attached to this letter are provided as electronic desk copies of the same information and are intended for distribution to Drs. Perlstein, Malozowski, and Gebert. Please note that the paper submission of this information is considered to be the archival copy.

In addition to the responses to the above requests, a copy of this letter *(cover.pdf)* is included on the CD-ROMs. The CD-ROMs have been scanned with Network Associate's McAfee Virus Scan for Windows version 4.0.3 and were found to be virus-free.

If there are questions regarding this information, please contact me by telephone at (616) 833-6717 or by fax at (616) 833-8237.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Cynthia J. Blanchard

Cynthia J. Blanchard
Regulatory Manager

CJB:kmv

NDA SUPP AMEND

Pharmacia&Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

ORIGINAL sel/031 BS

September 27, 2000

Division of Metabolism and Endocrine Drug Products HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-280/S-031
GENOTROPIN®
(somatropin [rDNA origin] for injection)

AMENDMENT
Statistical corrections

Dear Sir or Madam:

We refer to a telephone conversation on September 20, 2000, between Robert Perlstein, M.D., Medical Reviewer, and Cynthia Blanchard, Pharmacia & Upjohn. Dr. Perlstein relayed questions on behalf of Dr. James Gebert, Statistical Reviewer, regarding errors found during the review of NDA 20-280/S-031. The errors mentioned were found in item 8/10, Volume 23 (report of study 90-079 in Germany).

A document with the FDA observations and Pharmacia & Upjohn responses was prepared by our statisticians in Sweden, John Schoenfelder and Henrik Franzon, and is attached. We hope that this information is sufficient to address your concerns. If you would like to discuss these issues further we would be delighted to arrange a teleconference.

If there are questions regarding this information, please contact me by telephone at (616) 833-6717 or by fax at (616) 833-8237.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Cynthia J Blanchard

Cynthia J. Blanchard
Regulatory Manager

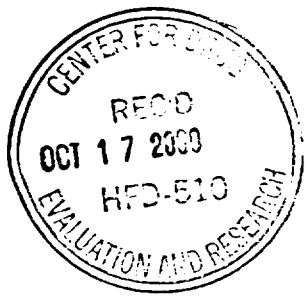
CJB:kmv

DUPLICATE

NDA SUPPLEMENT S-031-WD

Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000



October 16, 2000

Division of Metabolism and Endocrine Drug Products HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-280/S-031
GENOTROPIN®
(somatropin [rDNA origin] for injection)

EFFICACY SUPPLEMENT
Withdrawal of application

Dear Sir or Madam:

Pharmacia & Upjohn wishes to withdraw the above-referenced supplement to NDA 20-280 without prejudice to refiling.

If there are questions regarding this information, please contact me by telephone at (616) 833-6717 or by fax at (616) 833-8237. Please send correspondence addressed to Unit 0633-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Cynthia J Blanchard

Cynthia J. Blanchard
Regulatory Manager

CJB/crdt

Enclosure

Final Printed Label

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone (616) 833-4000

October 20, 2000

Division of Metabolism and Endocrine Drug Products HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-280
GENOTROPIN®
(somatropin [rDNA origin] for injection)

AMENDMENT
Request for Meeting

Dear Sir/Madam:

Pharmacia & Upjohn (P&U) requests a Type A meeting with the Division of Metabolism and Endocrine Drug Products to discuss rewriting the efficacy supplement for use of GENOTROPIN in the treatment of growth failure in children born small for gestational age (SGA). We consider this meeting to be immediately necessary for an otherwise stalled drug development to proceed.

The efficacy supplement for this indication, NDA 20-280/S-031, submitted June 30, 2000, and withdrawn October 16, 2000, will serve as background information for the meeting.

Pharmacia & Upjohn Company expects to gain a clear understanding of FDA concerns regarding the withdrawn application and mutual agreement on the presentation of data for the planned resubmission of this application.

A preliminary proposed agenda is as follows:

Agenda Item 1: 5 minutes
Introductions
Agenda Item 2: 75 minutes
Discussion
Agenda Item 3: 10 minutes
Wrap-up and summary of agreements

Specific questions P&U would like FDA to address include the following:

1. What are the specific issues that caused FDA to consider the application for SGA unapprovable?
2. What additional analyses would the reviewers like to see in a rewritten application?
3. What are other aspects of the submission that the Company can improve?

The following is a tentative list of P&U representatives who will attend the meeting:

Myrlene Staten, M.D.	Sr. Director, Metabolic Dis.Clinical Research
Birgitta Lange-Sjöblom, M.Sc.	Clinical Program Leader
Steven L. Schoenfeld, M.D.	Director, Metabolic Diseases Clin. Dev.
John Schoenfelder, Ph.D.	Director, Biostatistics and Data Management
Henrik Franzon, Ph.D.	Biostatistician
Donald Gieseker	Assoc. Director, Global Regulatory Affairs
Michael Burdick	Assoc. Director, Global Regulatory Affairs
Cynthia Blanchard	Regulatory Manager, Global Regulatory Affairs

A list of Agency staff requested by the sponsor to participate in the proposed meeting:

Medical Reviewer(s)
Biostatistician
CSO/Project Manager
Division Director

If you have any questions regarding this information, please contact me at by telephone (616) 833-6717 or fax (616) 833-8237. Please address correspondence to Unit 0633-298-113.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Cynthia J. Blanchard
Regulatory Manager

CJB:lmf

Nov. 2, 2000

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-280/S-031

Pharmacia & Upjohn Company
Attention: Cynthia J. Blanchard
Regulatory Manager
7000 Portage Road
Unit 0633-298-113
Kalamazoo, MI 49001-0199

Dear Ms. Blanchard:

We acknowledge receipt of your October 16, 2000, correspondence notifying us that you are withdrawing your June 30, 2000, supplemental new drug application for Genotropin (somatropin [rDNA origin] for injection).

We acknowledge receipt of your amendments dated July 31, August 9, and September 11, 15, and 27, 2000.

This supplement proposed a new indication to provide for long-term treatment of growth failure in children born small for gestational age (SGA).

Therefore, in accordance with 21 CFR 314.65, this supplemental application is withdrawn as of the date of our receipt of your notification, October 17, 2000. This withdrawal does not prejudice any future filing of the application. You may request that the information contained in this withdrawn supplemental application be considered in conjunction with any future submission.

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

Sincerely,

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Dec. 15, 2000

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-280

Pharmacia & Upjohn
Attention: Cynthia Blanchard
Regulatory Manager
Unit 0633-298-113
7000 Portage Road
Kalamazoo, MI 49001-0199

Dear Ms. Blanchard:

Please refer to the meeting between representatives of your firm and FDA on November 9, 2000. The purpose of the meeting was to discuss problems with supplement 031 (Small for Gestational Age).

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at 301-827-6423.

Sincerely,

/S/

Crystal King, P.D., M.G.A.
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Office of Orphan Products Development *(HF-35)*
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

December 27, 2000

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, Michigan 49001

Attention: Cynthia Blanchard
Regulatory Affairs

Dear Ms. Blanchard:

Reference is made to the orphan-drug application received March 30, 2000, submitted pursuant to Section 526 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb) for the designation of somatropin as an orphan drug (application #00-1354). Please also refer to your submission dated September 26, 2000.

We have completed the review of this application and have determined that somatropin qualifies for orphan designation for use in the long-term treatment of growth failure in children who were born small for gestational age (SGA).

Please be advised that if somatropin is approved for an indication broader than the orphan designation, your product might not be entitled to exclusive marketing rights pursuant to Section 527 of the FFDCA (21 U.S.C. 360cc). Therefore, prior to final marketing approval, sponsors of designated orphan drugs are requested to compare the designated orphan indication with the proposed marketing indication and to submit additional data to amend their orphan designation prior to marketing approval if warranted.

Finally, please notify this Office within 30 days of submission of a marketing application for the use of somatropin as designated. Also an annual progress report must be submitted within 14 months after the designation date and annually thereafter until a marketing application is approved (21 CFR 316.30). If you need further assistance in the development of your product for marketing, please feel free to contact John J. McCormick, M.D. at (301) 827-3666.

Please refer to this letter as official notification of designation and congratulations on obtaining your orphan-drug designation.

Sincerely yours,

John J. McCormick for

Marlene E. Haffner, M.D., M.P.H.
Rear Admiral, United States Public Health Service
Director, Office of Orphan Products Development

JAN 5 2001

ORIGINAL

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

NDA NO. 20-280 REF NO. S-31
NDA SUPPL FOR SE1

January 25, 2001

Division of Metabolism and Endocrine Drug Products HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
Attn: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

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

Re: NDA 20-280/S-031 (Resubmission)
GENOTROPIN®
(somatropin [rDNA origin] for injection)

EFFICACY SUPPLEMENT
Treatment of Growth Failure in Children Born Small for Gestational Age

Dear Sir or Madam:

Under the provisions of 21CFR 314.71, Pharmacia & Upjohn (P&U) is resubmitting an efficacy supplement to NDA 20-280, GENOTROPIN (somatropin [rDNA origin] for injection), to provide for long-term treatment of growth failure in children born small for gestational age. The original submission was submitted June 30, 2000 and withdrawn October 17, 2000, without prejudice for refiling.

Clinical Information
The clinical information provided in this supplement includes data from four pivotal studies performed in Belgium (TRN 90-080/98-8122-011), France (TRN 89-041), Germany, (TRN 90-079), and Nordic countries (TRN 89-070/89-017). The studies were of similar design, being open-label multi-center studies where patients were randomized into three parallel groups. Two of the groups were devoted to active treatment in different dosages, and the third group served as an untreated control.

In a meeting with the Agency on November 10, 1999, agreement was made that catch-up growth, as demonstrated in these four studies, is an acceptable primary efficacy variable in our sNDA for the use of GENOTROPIN in the treatment of growth failure in children born small for gestational age. In a meeting on November 9, 2000, subsequent to the withdrawal of the original application, FDA provided guidance regarding data presentations to be included in this resubmission. Sample tables provided to the Agency on December 8, 2000, were reviewed by Dr. Perlstein and considered acceptable for inclusion in this resubmission as discussed in a teleconference on

January 19, 2001. Additional data presentations also discussed during the same teleconference will be submitted by February 8, 2001, as an amendment to this supplement.

User Fee
Orphan drug designation was granted December 27, 2000, for this indication. The User Fee cover sheet and a copy of the letter from the Office of Orphan Product Development are included with this submission (see Volume 1, Item 18).

Application Format
An abbreviated Table of Contents for this application is attached to this letter. The more detailed Overall Index for this application is located in Volume 1, Item 1. The first volume of each item contains a comprehensive table of contents for that item. Each volume bears an overall volume number on the binder cover from 1 to 41.

Submission Information
Data are being provided in print or electronic format, as described below and on the attached abbreviated Table of Contents.

- Paper submission: archival and review copies of all volumes for Items 1, 2, 3, 8/10, 13/14, 16, 18, and 19. Two review copies of Item 8/10 are provided for the Clinical and Statistical reviews, respectively.

- Electronic submission: archival and review copies of Item 11 (Case Report Tabulations - CRT) and Item 12 (Case Report Forms - CRF) are being submitted on one CD-ROM in electronic form only. The Case Report Tabulations are in SAS transport file format. The total size of these electronic files is 65 megabytes. In addition, a copy of this letter (*cover.pdf*), a signed Form 356h (*356h.pdf*), and the abbreviated Table of Contents (*ndatoc.pdf*) are included on the CD-ROM. The CD-ROM, located in Volume 1, has been scanned with Network Associate's McAfee Virus Scan for Windows version 4.0.3a and was found to be virus free. One archival and one review copy of the CD-ROM are included in this submission.

If you have any questions regarding the content of this submission, please contact either Gregory A. Brier at (616)-833-3670 or me by telephone at (616) 833-6717. Our fax number is (616) 833-8237.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Gregory A. Brier /for
Cynthia J. Blanchard
Regulatory Manager

CJB/crdt
Enclosures

Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

January 31, 2001

Division of Metabolism and Endocrine Drug Products HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
Attn: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-280/S-031 (Resubmission)
GENOTROPIN®
(somatropin [rDNA origin] for injection)

DESKCOPY ON CD-ROM

Dear Sir or Madam:

Pharmacia & Upjohn (P&U) is submitting as requested four electronic deskcopies of NDA 20-280/S-031 GENOTROPIN (somatropin [rDNA origin] for injection) for SGA as a review aid. Each deskcopy is on a single CD-ROM and contains the following information:

Word97 Format

- Proposed labeling both clean and mark-up versions.
- Item 3 (appendixes not available).
- Item 8 (appendixes not available).
- Abridged Overall Index.

PDF Format

- Volumes 1-33 which include appendixes. Each volume is a separate PDF file. The PDF file hyperlinks work within each open volume, but not across volumes.
- Volumes 34-41 are also provided, but these files only contain an index to the publications included in the paper submission. Publications are not available electronically.
- In addition, a copy of the sNDA letter (*cover.pdf*) and the sNDA Form 356h (*356h.pdf*) are included on the CD-ROM.

Each CD-ROM has been scanned with Network Associate's McAfee Virus Scan for Windows version 4.0.3a and was found to be virus free.

If you have any questions regarding the content of this submission, please contact either Gregory A. Brier at (616)-833-3670 or me by telephone at (616) 833-6717. Our fax number is (616) 833-8237.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Gregory A Brier / for

Cynthia J. Blanchard
Regulatory Manager

CJB:mlw

Feb. 2, 2001

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-280/S-031

Pharmacia & Upjohn Company
Attention: Cynthia J. Blanchard
Regulatory Manager
7000 Portage Road
Kalamazoo, Michigan 49001

Dear Ms. Blanchard:

We acknowledge receipt on January 26, 2001, of your January 25, 2001, resubmission to your supplemental new drug application (Supplement-031) for Genotropin (somatropin [rDNA origin] for injection), which you withdrew on October 17, 2000.

This resubmission contains data from four clinical studies to support a new indication to provide for long-term treatment of growth failure in children born small for gestational age (SGA).

Your resubmission has been designated as a Priority (P) review.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on March 27, 2001, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be July 26, 2001.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). However, this requirement does not apply to designated orphan designations. Therefore, you need not submit this information.

If you have any questions, call me at (301) 827-6423.

Sincerely,

{See appended electronic signature page}

Crystal King, P.D., M.G.A.
Regulatory Project Manager
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ORIGINAL

Pharmacia & Upjohn

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA
Telephone: (616) 833-4000

March 21, 2001

Division of Metabolism and Endocrine Drug Products HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
Attn: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

SE1 031 BS
NDA SUPPL AMENDMEN

Re: NDA 20-280/S-031
GENOTROPIN®
(somatropin [rDNA origin] for injection)

Amendment
Response to FDA's March 12, 2001
Biostatistics Randomization Questions

Dear Sir or Madam:

Pharmacia & Upjohn (P&U) is submitting this Amendment to NDA 20-280, GENOTROPIN (somatropin [rDNA origin] for injection), Supplement S-031 in answer to two biostatistics questions by FDA (Dr. James Gebert) in a fax dated March 6, 2001, and subsequently sent and received by P&U on March 12, 2001.

P&U's response is presented in regular font and follows immediately after each FDA question. The two FDA's questions are identified by the use of bold italics font.

Question 1:
Please describe how the randomization was carried out in each of the studies. In particular, was blocked randomization used? Was there blinding of the persons assigning treatment to patients, persons taking height measurements, etc? How did a patient receive his randomized treatment? If there was a treatment packet, what did it contain?

Generation of randomization lists in each study

For each of the 4 studies, the randomization list and envelopes for each patient number were prepared by the Department of Biostatistics and Data Management at Pharmacia & Upjohn AB, Stockholm, Sweden. The randomization program and the source code are available for inspection upon request.

In study 89-041, patients meeting the eligibility criteria and willing to participate at an initial visit were allocated to the study groups according to a center-stratified computer-generated randomization list. The plan was to include 22 patients in the untreated group and 44 patients in each of the two treated groups. The randomization was generated using blocks of 5 (1+2+2) or 10 (2+4+4) depending on the expected number of patients at each center. Of the 22 centers that enrolled patients, 14 had a block size of 5 and 8 had a block size of 10.

In study 89-070, patients meeting the eligibility criteria and willing to participate at an initial visit were allocated to the study groups according to a computer-generated randomization list. The patients were stratified by country (Norway, Denmark, Finland and Sweden) and age (< 4 years and 7 months, ≥ 4 years and 7 months). The plan was to include 20 patients in the untreated group and 28 patients in each of the two treated groups. The randomization was generated using blocks of 19 (5+7+7).

In study 89-071, patients meeting the eligibility criteria and willing to participate at an initial visit were allocated to the study groups according to a computer-generated randomization list. The patients were stratified by country (Norway, Denmark, Finland and Sweden) and age (< 4 years and 7 months, ≥ 4 years and 7 months). The plan was to include 10 patients in the untreated group and 20 patients in each of the two treated groups. The randomization was generated using blocks of 10 (2+4+4).

In study 90-079, patients meeting the eligibility criteria and willing to participate at an initial visit were allocated to the study groups according to one central computer-generated randomization list (i.e. one list for all centers, no center-specific lists). The plan was to include 20 patients in the untreated group and 25 patients in each of the two treated groups. The randomization was generated using blocks of 14 (4+5+5).

In study 90-080, patients meeting the eligibility criteria and willing to participate at an initial visit were allocated to the study groups according to one central computer-generated randomization list (i.e. one list for all centers, no center-specific lists). The plan was to include 16 patients in the untreated group and 24 patients in each of the two treated groups. The randomization was generated using blocks of 8 (2+3+3).

Method of assigning patients to treatment groups

89-041

After informed consent was obtained and eligibility for the study was assessed, the data of the initial visit were documented on the Case Report Form (CRF). The first 3 pages of the CRF (date of birth, patient's initials and inclusion/exclusion criteria) was sent to and checked by the monitor at the Pharmacia & Upjohn Market Company in France. Sealed envelopes from the randomization, stored at Pharmacia & Upjohn, France, were opened in consecutive order by the clinical monitor (the date of randomization and initials were to be written on the envelope at the opening). The responsible investigator was then informed of the study group allocation.

Twelve patients were randomized but did not begin the study. For 4 of these patients the number was reassigned (01-04, 01-10, 01-14 and 10-02).

89-070

Norway, Denmark and Finland

After informed consent was obtained and eligibility for the study was assessed, the patient's birth date and initials were sent to the medical department at Pharmacia & Upjohn, Stockholm. Sealed envelopes from the randomization, stored at Pharmacia & Upjohn, Stockholm, were opened, signed and dated in consecutive order. The responsible investigator and the Market Company were then informed of the study group allocation.

Sweden

The patients were initially identified by the coordinating investigator. Before the eligibility for the study was assessed she assigned patient numbers (1 to 31) consecutively. These patient numbers were then retained in the database rather than the numbers from the randomization list. Since some of the originally identified patients were not randomized, the patients randomized do not have consecutive patient numbers.

After informed consent was obtained and eligibility for the study was assessed, the patient's birth date and initials were sent to the medical department at Pharmacia & Upjohn, Stockholm. Sealed envelopes from the randomization, stored at Pharmacia & Upjohn, Stockholm, were opened, signed and dated in consecutive order. The coordinating investigator received information about the study group allocation and subsequently informed the different centers.

89-071

Norway, Denmark, Finland and Sweden

After informed consent was obtained and eligibility for the study was assessed, the patient's birth date and initials were sent to the medical department at Pharmacia & Upjohn, Stockholm. Sealed envelopes from the randomization, stored at Pharmacia & Upjohn, Stockholm, were opened, signed and dated in consecutive order. The responsible investigator and the Market Company were then informed of the study group allocation.

90-079

Patients were initially identified with consecutive numbers at each center before the patient's consent was obtained and inclusion/exclusion criteria were checked. These patient numbers were then retained in the database rather than the numbers from the randomization list. Since some of the originally identified patients were not randomized, the patients randomized do not have consecutive patient numbers within each center.

After informed consent was obtained and eligibility for the study was assessed, the data of the background visit were documented on the CRF. The CRF was sent to and checked by the monitor at the Pharmacia & Upjohn Market Company in Germany and the coordinating investigator. Sealed envelopes from the randomization, stored at Pharmacia & Upjohn, Germany, were opened, signed and dated in consecutive order by the clinical monitor. The coordinating investigator and the responsible investigator were then informed of the study group allocation.

At the time of randomization for the first 7 patients, there was no monitor for the German study. For these patients the treatment allocation was administered from the medical department at Pharmacia & Upjohn, Stockholm. Information about the randomization was sent to the Market Company, which then informed the investigators.

90-080
After informed consent was obtained and eligibility for the study was assessed, the patient's birth date and initials were communicated from the principal investigator to the medical department at Pharmacia & Upjohn, Stockholm, via the Pharmacia & Upjohn Market Company in Belgium. Sealed envelopes from the randomization, stored at Pharmacia & Upjohn, Stockholm, were opened, signed and dated in consecutive order. Information about the randomization was sent to the Pharmacia & Upjohn Market Company in Belgium. The principal investigator received information about the study group allocation from the Market Company and subsequently informed the different centers.

Study medication distribution

The patients in all studies were educated by the investigator or a nurse how to use the injection devices. They received the study medication and the injection devices (pens, needles, training ampoules and written instructions) either from the investigator at the center or from the pharmacy.

As these studies were not blinded, the person who performed the height measurements could have known the treatment dose. When the measurements were done by the investigator him-/herself, the dose was definitely known.

Question 2:
There appears to be no relationship between the PID number within a center and Visit 0 dates. Please explain.

The actual randomization took place between an initial visit and the baseline visit. When the laboratory results were finalized and the patient's eligibility for the study was assessed, information about the patients were sent by mail to Pharmacia & Upjohn. The investigator was then informed of the study group allocation by a confirmation letter. The patients were to come to the baseline visit after the randomization, but the time between these occasions differed between patients. Thus, there is no direct relationship between the randomization numbers and the baseline dates.

If you have any questions regarding the content of this submission, please contact either Gregory A. Brier at (616)-833-3670 or me by telephone at (616) 833-6717. Our fax number is (616) 833-8237.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Gregory A. Brier /for
Cynthia J. Blanchard
Regulatory Manager

CJB:SEH

REVIEWS COMPLETED

CSO ACTION:

☐ LETTER ☐ N.A.I. ☐ MEMO

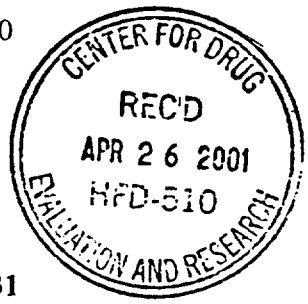
CSO INITIALS DATE

Pharmacia & Upjohn

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA
Telephone: (616) 833-4000

April 25, 2001

Dr. Robert Perlstein
Division of Metabolism and Endocrine Drug Products HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
Attn: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857



Re: NDA 20-280/S-031
GENOTROPIN®
(somatropin [rDNA origin] for injection)

ATTN: DR. ROBERT PERLSTEIN
DESK COPY Version 2

Dear Dr. Perlstein:

Please refer to a telephone conversation on April 10, 2001, with Greg Brier (Pharmacia & Upjohn) in regard to NDA 20-280/S-031, which was resubmitted January 25, 2001, for the use of GENOTROPIN for SGA. In response to your request, I have enclosed four copies of Desk Copy v.2, an electronic review aid on CD-ROM that contains the following:

1. A copy of this letter
2. A directory (N20280) containing two subdirectories:
   a) Original Desk Copy
   b) April 24, 2001 Amendment.

The subdirectory entitled "Original Desk Copy" contains all information previously submitted as an electronic review aid for the January 25, 2001, resubmission of S-031. The subdirectory entitled "April 24, 2001 Amendment" contains information submitted as a paper amendment to S-031.

Please note that "April 24, 2001 Amendment" contains a replacement of the Integrated Summary of Efficacy (ISE) Appendix 5, and that the earlier version of ISE Appendix 5 submitted in the January 25, 2001, submission of S-031 should be disregarded. The earlier version of ISE Appendix 5 has not been deleted from the "Original Desk Copy" subdirectory.

Four identical copies of Desk Copy v.2 (CD-ROM) are enclosed as electronic review aids intended for distribution to the reviewers of this application. Please note that the paper submission of the April 24, 2001 Amendment is considered to be the official archival copy.

Each CD-ROM has been scanned with Network Associate's McAfee Virus Scan for Windows version 4.0.3a and found to be virus free.

If you have any questions regarding this submission, please contact either Gregory A. Brier at (616)-833-3670 or me by telephone at (616) 833-6717. Our fax number is (616) 833-8237.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Cynthia J. Blanchard

Cynthia J. Blanchard
Regulatory Manager

CJB/crd

Enclosure

cc: Crystal King, Project Manager, Division of Metabolic and Endocrine Drug Products

ORIGINAL

Pharmacia & Upjohn

Pharmacia & Upjohn
7000 Portage Road
Kalamazoo, MI 49001-0199
USA
Telephone: (616) 833-4000

June 19, 2001

NDA SUPP AMEND
SE1-031-BM

Division of Metabolism and Endocrine Drug Products HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
Attn: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-280/S-031 (SGA)
GENOTROPIN®
(somatropin [rDNA origin] for injection)

AMENDMENT
Response to Requests for Information

Dear Sir or Madam:

Pharmacia & Upjohn (P&U) is submitting this Amendment to NDA 20-280/S-031 (SGA), to provide responses to requests for information discussed with FDA Medical Reviewer (Dr. Robert Perlstein) during telephone conversations on May 16, 17, 18, 29, and 30, June 1 and 6. In addition, we are providing a response to a request for information from Dr. James Gebert reported to P&U by Crystal King, FDA Project Manager on May 30, 2001.

Our responses are included in the enclosed attachments. The same information was submitted as an informal desk copy on CD-ROM to Dr. Perlstein and Dr. Gebert on June 8, 2001.

Attachment 1: Conversion tables:

- A copy of pages from Williams Textbook of Endocrinology, 8th Edition, discussed May 16 and 17, and June 1 with Dr. Perlstein.

Attachment 2: Revised ISS Appendix 10b:

- Revised ISS Appendix 10b, including normal ranges and units of measure for laboratory values, discussed May 16 and 17 with Dr. Perlstein. Please note that Centers 2 and 18 did not analyze IGF-1 at the center. Analyses were done at a Pharmacia & Upjohn laboratory, which did not have any normal ranges.

1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

Attachment 9: Number of study centers per study:

- A list of the number of centers per study submitted with the SGA application, requested by Dr. Perlstein on June 6.

Attachment 10: FDA and P&U contacts:

- A table of contacts between FDA and P&U in relation to this application, requested June 6 by Dr. Perlstein.

Attachment 11: Final height data:

- A written response to the question posed on June 7 regarding the Company's intent to document and submit final height data to FDA, requested by Dr. Perlstein on June 7.

If there are any questions regarding the content of this submission, please contact either Gregory A. Brier at (616)-833-3670 or me by telephone at (616) 833-6717. Our fax number is (616) 833-8237.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Cynthia J. Blanchard

Cynthia J. Blanchard
Regulatory Manager

CJB/crd

Attachments

ORIGINAL

Pharmacia & Upjohn
7000 Portage Road
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Telephone: (616) 833-4000

Pharmacia & Upjohn

July 2, 2001

Division of Metabolism and Endocrine Drug Products HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

SE1 031 SL
NDA SUPP AME

RE: NDA 20-280/S-031 (SGA)
GENOTROPIN®
(somatropin [rDNA origin] for injection)

AMENDMENT
SAFETY UPDATE

Dear Sir or Madam:

In accordance with 21 CFR §314.50(d)(5)(vi)(b), Pharmacia & Upjohn (P&U) is submitting a safety update report for GENOTROPIN®, NDA 20-280/S-031 (SGA). The same information was submitted as a desk copy on CD-ROM to Dr. Robert Perlstein, Medical Reviewer, on June 22, 2001.

In a conversation with Cynthia Blanchard, Regulatory Manager, on June 13, 2001, Dr. Perlstein, requested that the Safety Update be formatted exactly as the Integrated Summary of Safety (ISS) in NDA 20-280/S-031, and that it include the following:

1) assurance that the data are only new data, not overlapping the ISS
2) start and stop dates for the Safety Update
3) assurance that no programmatic errors exist
4) individual patient test results for nine safety parameters, to include patients outside normal ranges, along with normal ranges
5) an appendix with normal ranges.

In a subsequent conversation with Steven Schoenfeld, M.D., and Cynthia Blanchard held on June 18, 2001, Dr. Perlstein agreed to receive the Safety Update with previously requested information and a document comparing formats of the ISS and Safety Update. The table comparing the documents is found in Volume 1, Tab A, and the individual data are included in Volume 3, Tab D.

The following are responses to the above-listed requests:

1) This Safety Update includes new data from the NDA cut-off date (Month 72) up to, and including, December 31, 2000.
2) The cut-off date for clinical data from the original NDA submission was the 72-moth visit for each study. The first patient reached Month 72 on February 7, 1996, and the last patient reached Month 72 on June 10, 1999. This safety update report covers a study period of between 18 months to nearly 5 years.

3) Programmatic errors addressed in our June 19, 2001, submission of responses to reviewer requests, have been corrected, and data for the Safety Update were generated with corrected programs.
4) Individual test results including normal ranges for nine safety parameters are included in Volume 3, Tab D.
5) Appendix 11 contains normal ranges for laboratory tests.

During the process of adding normal ranges to the individual patient data listings, a few inconsistencies were noted and corrected in the units of measure. For example, nmol/l was changed to pmol/l (T4 free) and mIU/L was changed to mU/l (TSH). Please note that no numeric values were changed. The affected documents are in Individual Patient Data in the Additional Information section.

The Safety Update contains the following information:

- Comparison of format and content between the ISS and the Safety Update
- Text of the Safety Update
- Appendices 1 – 11
- Additional Information:
  - Individual Patient Data
    - Introduction (notation regarding correction of units of measure)
    - Nine listings of individual patient laboratory values for patients with values outside normal ranges and including normal ranges on the listing, one for each of nine safety parameters)
  - Lab Values by Treatment Group
    - Introduction
    - Lab Values Tables (lab values for 9 safety parameters by treatment group)
  - Table of CS and NCS (a table corresponding to ISS Tables 47, 48, and 49)

If you have any questions regarding this information, please call Greg Brier at (616) 833-3670 or Cynthia Blanchard at (616) 833-6717. Our fax number is (616) 833-8237.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Cynthia J. Blanchard

Cynthia J. Blanchard
Regulatory Manager

CJB:kmv

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Pharmacia & Upjohn
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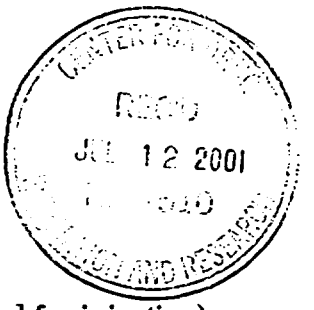
Telephone: (616) 833-4000

NDA SUPP AMEND
SE1-031 - BM

July 11, 2001



Division of Metabolism and Endocrine Drug Products HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-280/S-031
GENOTROPIN®
(somatropin [rDNA origin] for injection)

AMENDMENT
RESPONSES TO MEDICAL REVIEWER

Dear Sir or Madam:

Pharmacia & Upjohn (P&U) is submitting this Amendment to NDA 20-280, GENOTROPIN (somatropin [rDNA origin] for injection), Supplement S-031 in response to questions from FDA Medical Reviewer (Dr. Perlstein) discussed during a teleconference on Friday, July 6, 2001 with P&U representatives Cindy Blanchard and Greg Brier.

The following responses to FDA questions are included in this Amendment:

ISS QUESTIONS:

1. Scatter Graphs Patients N, Month 0-12 Vs. Revised Table 47 Patient N, Month 0-12.
2. Thyroid Concerns
   a) Number of patients hypothyroid and on stable thyroid replacement at baseline.
   b) An accounting of patients treated for hypothyroidism during the trial period, including additional information on patient 906-03 in study 90-079.
      1. Patient 906-03, study 90-079
      2. Patient 08-02, study 89-041
      3. Patient 10-01, study 89-041

SAFETY UPDATE REPORT:

1. Omission of References to NCS in the Safety Update.
2. Details of Two Patients with Prominent Chin/Prominent Jaw Adverse Events
3. Details of patient 07-420, study 89-070 who experienced benign intracranial hypertension
4. Glucose Related Issues
   a) Patient 902-08, study 90-079, elevated HbA1c and 2 elevated IGF-1 values
   b) Patient 862-02, study 90-079 elevated insulin at 120 minutes
   c) Patient 06-07, study 89-041 elevated glucose
5. Details of Patient 04-04 in Study 879-041 with Elevated Testosterone and Virilism
6. Details of Patient 801-02 in Study 90-079 (Germany) with Precocious Puberty
7. A Summary of Patient Narratives in Table Format

If there are questions about this information, please call Greg Brier at (616) 833-3670 or me at (616) 833-6717 or. Our fax number is (616) 833-8237.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Gregory A. Brier /for

Cynthia J. Blanchard
Regulatory Manager

ORIGINAL

Pharmacia & Upjohn

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Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

RECEIVED
JUL 13 2001
CDR/CDER

SUPPL NEW CORRESP

S21-031-C

July 12, 2001

Central Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, MD 20852

Re: NDA 20-280/S-031
GENOTROPIN®
(somatropin [rDNA origin] for injection)

Electronic Submission
AMENDMENT Revised Package Insert

Dear Sir/Madam:

This regulatory submission in electronic format transmits Pharmacia & Upjohn (P&U) agreement of the package insert language and amends NDA 20-280, GENOTROPIN (somatropin [rDNA origin] for injection), Supplement S-031. Supplement S-031 provides for a new indication: Long-term treatment of growth failure in children born small for gestational age (SGA) who fail to manifest catch-up growth by age 2.

The CD-ROM has been scanned with Network Associate's McAfee Virus Scan for Windows version 4.0.3a and was found to be virus free. The CD-ROM contains the following files:

Root Directory – N20280

- Cover Letter
- 356h Form –
- Table of Contents –

Subdirectory – Labeling

- Highlighted Package Insert –
- Package Insert Clean Copy –
- Labeling Table of Contents –

Please use the clean copy of the package insert to indicate any further revisions.

If you have any questions regarding the content of this submission, please contact either Gregory A. Brier at (616)-833-3670 or me by telephone at (616) 833-6717. Our fax number is (616) 833-8237.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Gregory A. Brier /for
Cynthia J Blanchard
Regulatory Manager

CJB:SEH
Attachments

cc: (letter only)
Ms Crystal King, FDA Project Manager
Division of Metabolism and Endocrine Drug Products HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
Attn: Document Control Room 14B-19
5600 Fishers Lane
Rockville, MD 20857

DUPLICATE

Pharmacia & Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

July 13, 2001

Division of Metabolism and Endocrine Drug Products HFD-510
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

SE1 031 BM.
NDA SUPP AMEND

Re: NDA 20-280/S-031
GENOTROPIN®
(somatropin [rDNA origin] for injection)

AMENDMENT
RESPONSES TO MEDICAL REVIEWER

Dear Sir or Madam:

Pharmacia & Upjohn (P&U) is submitting this Amendment to NDA 20-280, GENOTROPIN (somatropin [rDNA origin] for injection), Supplement S-031. This Amendment is in response to comments from FDA Medical Reviewer (Dr. Perlstein) discussed during two teleconferences:

- Wednesday, July 11, 2001 with Greg Brier regarding the July 11, 2001 Amendment, and
- Thursday, July 12, 2001 with Cindy Blanchard regarding two additional review questions.

P&U responses to FDA questions are provided below:

Response to FDA's ISS Questions on the July 11, 2001 Amendment:

FDA Question:

2. Thyroid Concerns:

   a) TSH values for patients 805-01, and 906-03 in study 90-606-079; and patients 08-02 and 10-01 in study 89-041.

P&U Response:

TSH was obtained in trials 89-070/071 and 90-080 but was not obtained in trials 90-079 and 89-041. Therefore, TSH is not available for these patients.

If there are questions about this information, please call Greg Brier at (616) 833-3670 or me at (616) 833-6717 or. Our fax number is (616) 833-8237.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Gregory A. Brier/for

Cynthia J. Blanchard
Regulatory Manager

CJB:SEH

Pharmacia&Upjohn

7000 Portage Road
Kalamazoo, MI 49001-0199
Telephone: (616) 833-4000

July 23, 2001

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

Re: NDA 20-280/S-031
GENOTROPIN®
(somatropin [rDNA origin] for injection)

AMENDMENT
POSTMARKETING COMMITMENTS

Dear Dr. Orloff:

Pharmacia & Upjohn (P&U) is submitting this Amendment to NDA 20-280/S-031 to describe two postmarketing commitments: 1) to follow children enrolled in the four Small for Gestational Age (SGA) studies in order to obtain and submit their final height results; and 2) to compare the safety profile of patients receiving doses of somatropin greater than or equal to 0.4 mg/kg/week with the safety profile of patients receiving doses of somatropin less than 0.4 mg/kg/week.

Proposed Postmarketing Commitments:

Postmarketing Commitment #1:

P&U commits to extend all reasonable efforts to follow all patients (including those who dropped out of any of the four pivotal studies at any time point for any reason to the greatest extent possible) until they have reached final height, (defined as a growth rate of less than 2 cm/year) - as specified in the following Protocol Amendments:

- CTN 90-080 (Belgium), GENOTROPIN In Short Children Born Small For Gestational Age - A Long-Term Study In Belgium. A Randomized, Open, Parallel Groups, Multi-Center Study, Long-Term Extension Protocol CTN 98-8122-011, April 7, 1999,

- CTN 89-041 (France), Growth Hormone Treatment in Short Children Born Small for Date. An Open, Randomized, Parallel, Multicenter Study, Protocol Amendment No. 12, November 26, 1998,

- CTN 90-079 (Germany), GENOTROPIN in Children Short for Gestational Age - Safety and Efficacy. An Open Randomized, 3-Parallel Groups, Multicenter Study, Protocol Amendment No. 7, February 9, 1999, and

- CTN 89-070 (Nordic), GENOTROPIN in Short Children Born Small for Gestational Age, Protocol Amendment No. 6, November 26, 1998.

In this regard, P&U further commits to submit a report on the final height results within six months after the youngest child has reached final height. The submission of the final height report is estimated for December 2008. An interim report on final height results obtained through December 31, 2005 will be submitted by June 30, 2006.

Postmarketing Commitment #2:

P&U commits to provide Periodic Safety Reports in accordance with 21 CFR 314.80(c)(2) which include separate and distinct sections which describe the spontaneous event reports and safety information from the Kabi International Growth Survey (KIGS) for patients receiving doses of somatropin greater than or equal to 0.4 mg/kg/week. These sections will then compare the safety profile of these patients with the safety profile of patients receiving doses of somatropin less than 0.4 mg/kg/week (excluding Turner's syndrome and chronic renal insufficiency patients). The reporting period for Periodic Safety Reports containing these sections will commence immediately following the commercial launch of the SGA regimen and continue for four years.

If there are questions about this information, please contact Greg Brier at (616) 833-3670 or me at (616) 833-6717. Our fax number is (616) 833-8237.

Sincerely,

PHARMACIA & UPJOHN COMPANY

Gregory A. Brier /for

Cynthia J. Blanchard
Regulatory Manager

CJB:SEH