CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-280/S-031

ADMINISTRATIVE DOCUMENTS

PATENT INFORMATION AND CERTIFICATION

Pharmacia & Upjohn does not claim patents for this sNDA application, nor does the Company infringe on the patents of others. A patent search has been performed to confirm this statement. Original patent information can be found in approved NDA 20-280.

Please note that Pharmacia & Upjohn was granted an orphan drug designation for this indication on December 27, 2000 (application 00-1354).

EXCLUSIVITY SUMMARY for NDA # 21-106 SUPPL # 031

Trade Name Genotropin Generic Name: somatropin [rDNA origin] for injection
Applicant Name Pharmacia & Upjohn Co.
HFD- 510
Approval Date July 25, 2001

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

   a) Is it an original NDA? YES/___/ NO /__✓_/

   b) Is it an effectiveness supplement? YES /__✓_/ NO /___/

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

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

      YES /__✓_/ NO /___/

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

      N/A

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

d) Did the applicant request exclusivity?

YES /_✓__/NO /___/

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

7 YEARS ORPHAN EXCLUSIVITY_____

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /__✓_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC) Switches should be answered No - Please indicate as such).

YES /___/ NO /_✓__/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_✓__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)**N/A: NOT A NEW CHEMICAL ENTITY**

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

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

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

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

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

   YES /_✓__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_✓__/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_✓__/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /__✓_/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_✓__/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # CTN: 89-041

Investigation #2, Study # CTN: 89-070/89-071

Investigation #3, Study # CTN: 90-079

Investigation #4, Study # CTN: 90-080/98-8122-011

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 /_✓__/
Investigation #4	YES /___/	NO /_✓__/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_✓__/

Investigation #2 YES /___/ NO /_✓__/

Investigation #3 YES /___/ NO /_✓__/

Investigation #4 YES /___/ NO /_✓__/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #1, Study # CTN: 89-041

Investigation #2, Study # CTN: 89-070/89-071

Investigation #3, Study # CTN: 90-079

Investigation #4, Study # CTN: 90-080/98-8122-011

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? **N/A**

Investigation #1, 2, 3, 4

IND # _____ YES /___/ ! NO /_✓__/ Explain: all were foreign studies not carried out under an IND.

(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, 2, 3, 4:

YES /_✓__/ Explain _____ ! NO /___/ Explain Applicant sponsored all studies.

(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: _____

Preparer:

See appended electronic signature page
Crystal King, P.D., M.G.A.
Regulatory Project Manager

See appended electronic signature page
David Orloff, M.D.
Division Director

cc:
Archival NDA
HFD- /Division File
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

DEBARMENT CERTIFICATION FOR GENOTROPIN
(Children born small for gestational age [SGA])

Supplement to NDA 20-280
Protocols #89-041, 89-070/071, 90-079 and 90-080/98-8122-011

Pursuant to section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, the applicant certifies that, the applicant did not and will not use in any capacity the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act in connection with this application.

Ed L Patt

12/29/2000

Ed L. Patt
Associate Director
GRA Product Support - CMC

Date

MEMORANDUM

Date: June 19, 2001

To: Crystal King
Division of Metabolic and Endocrine Drug Products

From: Margie Kober
Division of Drug Marketing, Advertising, and Communications

RE: Genotropin draft labeling

I have reviewed the draft labeling for Genotropin and offer the following comments. Please share them with the rest of the team as you see fit. Thank you again for consulting DDMAC.

The introductory section of "Clinical Pharmacology" states...

> "In pediatric patients who have growth hormone deficiency (GHD) or Prader-Willi syndrome (PWS) or who were born small for gestational age (SGA), treatment with GENOTROPIN [redacted]"

The clinical studies section, however, only shows growth results in SGA studies. [redacted] If this outcome was not measured, I would recommend that it be deleted from the labeling. If it was, it should be included in the clinical studies section.

Table 4 includes data derived from study of a dose (0.7) that is higher than the recommended dose for this condition. Generally, we don't like to see unapproved doses anywhere in the labeling as they can make their way into promotional materials if they are included.

To: NDA 20-280/S-031

From: Robert S. Perlstein MD, Medical Officer

CC: Saul Malozowski MD, Team Leader

Crystal King, Project Manager

Date: 07/17/01

Re: Review of Safety Update Report

The Safety Update Report (SUR) for NDA 20-280/S-031 was submitted on 25Jun01 by the Sponsor, Pharmacia & Upjohn Company, Kalamazoo, MI. The SUR includes new safety data for the 4 open label extension studies (CTN 89-041 - France; CTN 90-079 - Germany; CTN 90-080/98-8122-011 - Belgium; and CTN 89-070/89-071 - Nordic countries) from Month 72 for any given patient through 31Dec00. Since the first patient reached Month 72 on 7Feb96 and the last patient reached Month 72 on 10Jun99, this SUR covers an additional study period ranging between ~18 months to ~5 years. An analysis of this safety data can be found in the Medical Officer's NDA review in Section VI.D.

/S/

Robert Perlstein MD, FACP, FACE
Medical Officer

/S/

Saul Malozowski MD, PhD
Team Leader

CC: Original NDA 20-280/S-031; HFD-510 NDA 20-280/S-031
HFD-510 RPerlstein, SMalozowski, JGebert, TSahlroot, CKing

To: NDA 20-280/S-031

From: Robert S. Perlstein MD, Medical Officer

CC: Saul Malozowski MD, Team Leader

Crystal King, Project Manager

Date: 07/17/01

Re: Acceptance of Sponsor's 12Jul01 Version of Revised Label

I agree with the 12Jul01 version of the Sponsor's proposed label.

/S/

Robert Perlstein MD, FACP, FACE
Medical Officer

/S/

Saul Malozowski MD, PhD
Team Leader

CC: Original NDA 20-280/S-031; HFD-510 NDA 20-280/S-031
HFD-510 RPerlstein, SMalozowski, JGebert, TSahlroot, CKing

Memorandum

Date: 7/17/01

From: Saul Malozowski
Medical Team Leader

Subject: Genotropin, Somatropin, (NDA 20-280/S-031.) To support an indication for short stature in children born small for gestational age (SGA)

To: David Orloff
Division Director, DMEDP

This memo is to support Dr. Perlstein's recommendations for this submission.

A small group of children that are born small for gestational age (SGA) fail to normalize their stature and remain small during infancy and adulthood. The underlying mechanism for this failure to thrive is unknown. Growth hormone (GH) has been shown to be safe and effective in increasing short-term growth in short children affected by numerous conditions. Among those we could list GH deficiency, chronic renal insufficiency, Turner's syndrome, and Prader Willie syndrome. Final height has also been shown to improve in GH deficient children and in girls with Turner's syndrome. Reports in the literature suggest that even normal short children could improve their final height when treated with GH. The safety of this maneuver has not been formally evaluated in these normal children. It is yet unknown whether the final height for all other listed conditions will improve, but the results evaluated suggest that a similar pattern of accelerated growth velocity was observed in studies previously evaluated at the FDA, and that predicated final height is indeed increased for all these conditions when GH therapy is given.

This NDA supplement provided information of the effects of Genotropin in children born SGA. Growth velocity, height SDS, final predicted height, and other growth parameters improved in children treated with Genotropin when compared to controls. No undue advancement of bone age was observed. Several studies replicated the results of the largest study.

As in previous studies using GH to increase height, adverse events were minor and similar to those already listed in the package insert. Neither the sponsor nor Dr. Perlstein attributed to GH any new or previously unrecognized adverse events.

There were, however, several patients treated with GnRH agonists. One of these patients may have developed central precocious puberty. No information is available to attribute this to GH. The others patients that received GnRH were most likely treated in an attempt to delay puberty and further increase their growth potential.

In the extension studies one patient developed intracranial hypertension, a complication listed in the package insert. Scoliosis and gynecomastia were also observed during the studies.

One patient receiving GH developed diabetes; several experienced glucose elevations throughout the study without any definitive pattern. GH is known to produce insulin resistance, and this is also listed in the current package insert. Whether or not insulin resistance and the potential for development of diabetes will be exacerbated by GH in these children already prone to have an increased susceptibility to manifest this condition remains unknown. In my view, this issue is the most important and has not been addressed in these studies and, in earnest, could not be addressed in registration studies.

In summary, a modest growth increase was seen in SGA patients treated with GH with an adequate safety profile.

Recommendations:

I recommend the approval of this product.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research

DATE: July 23, 2001

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 20-280/S-031

SUBJECT: sNDA review issues and recommended action

Background
Of the approximately 2.5% of children who are born small for gestational age (SGA), 10-15% fail to "catch up" by age 2, such that they have a height SDS below -2. Height SDS is defined as the patient's height minus the mean height for age in the population, with the difference divided by the standard deviation of the mean height for age in the population. Thus, it is a calculation of the number of standard deviations away from the population mean for age that the individual patient is at that age. Children who do not "catch up" by age 2, if left untreated, are destined, in many cases to have compromised final height, relative to the norm for the population. The studies presented in the current sNDA follow on investigations over the last decade indicating an effect of GH supplementation in children born SGA to enhance growth velocity, height SDS, and predicted adult height. Data on final stature are lacking at this time. Finally, of concern in treating these children, aside from the known adverse effects of GH therapy, is a risk of accelerating bone age beyond chronological age, with the possibility of precipitating precocious puberty and compromising final stature on that basis.

Medical
Efficacy
As described in detail in the Medical Officer's review, there were 4 similarly designed pivotal trials in the current package (all conducted in southern Europe and Scandinavia) in non-GHD children born SGA with failure to manifest catch-up growth by age 2. These were 6-year, open-label, randomized trials, with an untreated control group for the first 2 years. The doses of somatropin were 0.033 mg/kg/day (n=76), 0.067 mg/kg/day (n=93), and 0.1 mg/kg/day (n=18). The sponsor has proposed a recommended dose of 0.067 mg/kg/day.

Efficacy analyses included change from baseline in height velocity SDS, height SDS based on chronological age, height SDS based on bone age, and bone age-to-chronological age ratio (BA:CA). Dr. Perlstein has reviewed in detail the efficacy results with pooled results for height SDS based on chronological age at baseline and month 24 (end of the controlled period) summarized in table 24 on page 85 of his review. This endpoint, though not the primary efficacy variable as prospectively defined, was nevertheless chosen as that to be presented in labeling

based on internal discussions that concluded that these would be most readily understood by prescribers. These data form the basis for table 4 of the label.

In short, at the end of two years, starting at a baseline mean height SDS of –3.3 across all treatment groups, somatropin-treated patients exhibited a response to drug such that mean height SDS ranged from 1.2 (0.033mg/kg/day) and 1.7 (0.067 mg/kg/day) compared to 0.1 in the untreated group. The difference between the two somatropin groups was significant. There were insufficient numbers treated with the 0.1 mg/kg/day to reach any conclusions regarding efficacy or safety. Of further note, the mean BA:CA ratio did not exceed 1.0 for either treatment group at month 24, suggesting a favorable impact on final height, though this was not demonstrated. Finally, Dr. Perlstein notes the finding that most children exhibited a slow down of growth and a loss of height relative to mean for age with discontinuation of therapy after 2-3 years of treatment. Most of those restarting therapy (albeit a small group) exhibited catch-up growth anew.

Safety
The exposure in these trials was substantial, with 180 patients receiving somatropin for at least 2 years, 99 receiving treatment continuously from year 2 through year 6, 62 patients treated continuously for 6 years, and 50 patients treated continuously for 8 years. There were no deaths. The adverse event profile in these patients was consistent with that seen in other treated populations and consistent with the label for somatropin and other GH products. Dr. Perlstein highlights several of these adverse events including abnormal glucose tolerance, scoliosis, precocious puberty, change in pigmented nevi, and acromegaloid facial features. These AEs are discussed in the label.

Labeling
A final label has been negotiated and accepted by the Division.

Biopharmaceutics
There were no new biopharmaceutics studies submitted.

Pharmacology/Toxicology
No new pharmacology/toxicology studies were submitted.

Chemistry/ Microbiology
This is an approved drug product. No new CMC information or microbiology information was needed or submitted.
There were no establishment inspections.
A categorical exclusion from the environmental assessment was claimed by the sponsor and accepted by the Agency.

DSI/Data Integrity
The clinical audits resulted in recommendations to accept the data from the sites audited.

Financial disclosure

Dr. Perlstein has reviewed the financial disclosure information and finds no reason to question the integrity of the application on the basis of financial conflicts of interest.

Phase 4 recommendations
Dr. Perlstein has recommended two phase 4 commitments. The first requires that the sponsor make every effort to follow up the patients enrolled in the 4 phase 3 studies to assess final height. I do not think that this need be a phase 4 commitment. I recommend that it be requested/suggested in the action letter.

The second proposal is for a commitment to create a section in the periodic safety reports that describes the spontaneous adverse event reports from the Kabi International Growth Survey (KIGS) for patients receiving a dose of somatropin greater than 0.4 mg/kg/week. This section will compare the safety profile in this dosage range to that among patients treated with doses less than 0.4 mg/kg/week. This, too, can simply be a request in the action letter.

Recommendation
This application may be approved. No phase 4 commitments are required.

rmation Page

NDA 20-280-031
Page 1 of 2

o NOT send this page with the letter

RECORD OF TELEPHONE CONVERSATION/MEETING	Date: October 3, 2000
FDA participants: David Orloff, M.D., Division Director Saul Malozowski, M.D., Ph.D., Medical Team Leader Robert Perlstein, M.D., Medical Reviewer Todd Sahlroot, Ph.D., Biostatistics Team Leader Jim Gebert, Ph.D., Biostatistics Reviewer Crystal King, P.D., M.G.A., Regulatory Project Manager This telecon was placed to discuss data integrity with the small for gestational age (SGA) efficacy supplement. D. Orloff indicated that although our reviewers had spent a great deal of time attempting to review the application, due to qualitative concerns with the presented data, they are unable to do a substantive review. Had the extensive nature of these data concerns been clearer prior to the filing date, we would not have accepted the submission for filing. At this point in the review cycle, the Division does not believe we could approve the submission. We would not have sufficient time to review a major amendment prior to the action date. R. Spivey clarified that a NA decision would be due to the Division having no confidence in the data as presented. He then reviewed the options of (1) sending in a major amendment in the future; (2) receiving a NA action; (3) withdrawal and future resubmission. There would be no further User Fee charge for a resubmission following a withdrawal. D. Gieseker asked whether a priority review clock would still be granted under option 3. The Division responded in the affirmative. The Division indicated that we were willing to work with Pharmacia to discuss the details of the data problems encountered and to suggest additional analyses that would be helpful. The meeting would follow the regular meeting guidelines and could be held within one to two months following the request.	**NDA#:** 20-280 **Telecon/Meeting initiated by:** O Applicant/Sponsor ● FDA **By:** Telephone **Product Name:** Genotropin **Firm Name:** Pharmacia & Upjohn Co. **Name and Title of Person with whom conversation was held:** See attached list **Phone:** 616-833-6717

INFORMATION PAGE
ns on the next page

D. Orloff concluded the telecon by reiterating that the Division is anxious to cooperate with Pharmacia. /S/ 10-5-00 **David Orloff, Meeting Chair** /S/ 10/5/00 **Crystal King, Recorder**	

Attachment

cc: NDA 20-280
Div Files
HFD-510: D.Orloff/S.Malozowski/R.Perlstein/T.Sahlroot/C.King
HFD-715: J.Gebert

MEMORANDUM OF TELECON

DATE: January 19, 2001

APPLICATION NUMBER: NDA 20-280/S-031, Genotropin (somatropin [rDNA origin] for injection)

BETWEEN:

Name: Myrlene Staten, M.D., Sr. Director, Metabolic Diseases Clinical Development
Steven Schoenfeld, M.D., Director, Metabolic Diseases Clinical Development
John Schoenfelder, Ph.D., Director, Biostatistics and Data Management
Henrik Franzon, Ph.D., Statistician, Biostatistics and Date Management
Ronald Garutti, M.D., VP, Global Regulatory Affairs
Michael Burdick, Associate Director, Global Regulatory Affairs
Cindy Blanchard, Regulatory Manager, Global Regulatory Affairs

Representing: Pharmacia & Upjohn Co.

AND

Name: Crystal King, P.D., M.G.A., Regulatory Project Manager
Robert Perlstein, M.D., Medical Reviewer

Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: Draft data presentation sent by P&U on December 8, 2000, for SGA supplement re-submission.

FDA requested: (1) delineation of the uncontrolled, 2 to 6 year studies; (2) the addition of parameters to flow diagrams/tables to describe start to stop--specifically, baseline SDS, change from start to stop, and SDS at stop expressed as means and for individuals (e.g., same as for stop to restart); (3) expansion of the tables to stratify individuals to track SDS from start to stop to restart to final.

P&U agreed to submit the information as an amendment within two weeks following the initial supplement re-submission. The target date for the re-submission is January 26-29, 2001.

Crystal King, P.D., M.G.A.
Regulatory Project Manager

Meeting Minutes

NDA # and Drug Name:	NDA 20-280 S-031 Genotropin (somatropin [rDNA origin])
Meeting Date:	November 9, 2000
Time:	10:30 am
Location:	Parklawn Conference Room 12B-02
Indication:	Growth Hormone Deficiency for children born Small for Gestational Age (SGA)
Sponsor:	Pharmacia & Upjohn Co.
Type of Meeting:	Guidance
Sponsor Contact:	Cindy Blanchard @ 616-833-6717
Regulatory Project Manager:	Crystal King @ 301-827-6423
FDA Participants:	Saul Malozowski, M.D., Ph.D., Medical Team Leader
	Robert Perlstein, M.D., Medical Reviewer
	James Gebert, Ph.D., Biometrics Reviewer
	Crystal King, P.D., M.G.A., Regulatory Project Manager
	Samuel Wu, Pharm.D., Regulatory Project Manager
Sponsor Participants:	Myrlene Staten, M.D., Senior Director, Metabolic Diseases Clinical Research
	Birgitta Lange-Sjoblom, M.Sc., Clinical Program Leader
	Steven Schoenfeld, M.D., Director, Metabolic Diseases Clinical Development
	John Schoenfelder, Ph.D., Director, Biostatistics and Data Management
	Henrik Franzon, Ph.D., Biostatistician
	Donald Gieseker, Associate Director, Global Regulatory Affairs
	Michael Burdick, Associate Director, Global Regulatory Affairs

Meeting Objective: To explore the Division's concerns with the withdrawn supplement and to discuss data presentation for resubmission.

Background: Pharmacia submitted this supplement for SGA on June 30, 2000. Due to various Division concerns with the submission and the integrity of the presented data, the Division notified Pharmacia on October 3, 2000, that we would be unable to approve the supplemental indication. Pharmacia decided to

withdraw the supplement effective October 17, 2000. Subsequent to the withdrawal, the Division offered to discuss review concerns encountered during its evaluation.

No meeting package was requested by the Agency. Pharmacia requested that the following questions be discussed:

(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 re-written application?

(3) What are other aspects of the submission that the company can improve?

Following introductions, FDA presented responses to the questions. The responses were grouped into three discussion areas—Clinical, Statistical, and Document Preparation—and were presented in overhead format at the meeting. Additional significant points are summarized in *italics*.

The Division noted that examples given are problems noted during our review. Since an exhaustive review was not completed, we do not assume these are the only errors in the submission.

Clinical

Item 1: Please ensure that tables delineating patient disposition and reasons for discontinuation are easy to follow and contain numbers which are consistent with the text and subsequent tables.

Item 2: In the French study, the number of patients who developed precocious puberty requiring treatment with LHRH analogue therapy is unclear – the data appearing on pages 37, 42, and 70 of the study report conflict with each other.

Item 3: In the French study report, Figure 3 (page 55) and Figure 4 (page 56) demonstrate the effects of rhGH on height SDS and the change in height SDS during 72 months of treatment. For each treatment arm, data from the same patients only should be utilized at all time points. Otherwise, these graphs may be misleading.

Item 4: Please include the summary tables for the primary and secondary efficacy variables in the ISE (as constructed and submitted at the Agency's

request subsequent to the original submission). Please include HV SDS in the PP 0-24 month population.

The submission had only height, not HV SDS, in the PP 0-24 month population. We would like to see the four studies presented side-by-side, then as a conglomerate.

Item 5: In each individual study report and in the ISE (use summary tables as in #4), when analyzing HV SDS (after 1 and 2 years of therapy) and height SDS (after 2 years of therapy) results in the ITT and PP 0-24 month populations, please include regression analyses utilizing relevant covariates (i.e., age at initiation of rhGH therapy, baseline height SDS, baseline HV SDS).

Additional covariates of interest may certainly be included. This may not impact on the label, since these variables were not stated ahead of time.

Item 6: In the ISE and each individual study report (use summary tables as in #4), please indicate the distribution of HV SDS responses after 1 and 2 years of therapy (i.e., % in each treatment arm with HV SDS >+1, >+2, >+3,...), and the distribution of height SDS responses after 2 years of therapy (i.e., % in each treatment arm with height SDS >-2, >-1, >0, >+1, ...) when analyzing HV SDS and height SDS results in the ITT and PP 0-24 month populations.

This will enable us to have a sense of the distribution. If the results can be tested, that would be fine; otherwise display is sufficient.

Item 7: With regard to the additional supportive data for study years 2-6 regarding the number of patients who were discontinued from rhGH therapy and then restarted on rhGH therapy (submitted at the Agency's request subsequent to the original submission), please provide more detail.

We are especially interested in the French and Belgium patients discontinued per protocol. Even though the data is uncontrolled and my not be acceptable for the label, we would like the additional detail. Perhaps a controlled post-marketing study will be indicated.

Item 8: In the resubmission, please include your responses to the 1996 objections of the European Agency for the Evaluation of Medicinal Products.

This must be addressed in the reviews, so we need a summary of the European Agency findings. We have precedent for using different criteria than the final height, for example, the approvals for Praeder-Wili syndrome and chronic renal insufficiency.

In general, please include the coding of the tests and anything which we requested subsequent to the initial submission with the initial re-submission.

Statistical

Item 1: In Table 13 (vol. 20, page 37) the Month 0-12 column is misordered.

Table 13. Effects of somatropin on height velocity SDS during 2 years of treatment. PP 0-24 population.

Treatment group	Pretreatment N Mean (SD)	Month 0-12 N Mean (SD)	Month 12-24 N Mean (SD)
0.033	16 -1.5 (0.7)	11 -1.2 (0.9)	16 0.9 (1.2)
0.067	18 -1.1 (0.9)	16 2.4 (1.4)	18 2.6 (1.5)
Untreated	11 -1.3 (0.8)	18 4.0 (1.5)	11 -1.5 (0.6)
Primary analysis (Dunnett's test *): 0.033 vs. untreated		p=0.0001 S	p=0.0001 S
0.067 vs. untreated		p=0.0001 S	p=0.0001 S
Sec. analysis (Student's t-test): 0.067 vs. 0.033		p=0.0010	p=0.0002

* The p-values in the tables are not adjusted for multiple comparisons. The "S" implies statistical significance even after corrections for multiple comparisons. See also sect. 9.8.2.

There were, in general, too numerous mistakes with such a small sample. Thus, we question the whole quality assurance process.

Item 2: In Study TRN-079, the p-values given below table 9 did not agree with the p-values in table 9 (vol.23/ page 41). {This might possibly be explained by the Bonferroni and Dunnett's correction, but it was not clarified in the submission.} Other studies were not so corrected.

- During the 1st year of treatment the mean height velocity SDS was greater in both somatropin groups compared to the untreated group. The differences were statistically significant (p=0.0001).

- During the 2nd year of treatment the mean height velocity SDS was greater in both somatropin groups compared to the untreated group. The difference was statistically significant for the 0.067 group (p=0.0015), but not for the 0.033 group (p=0.0591).

Table 9. Effects of somatropin on height velocity SDS during 24 months of treatment.

ITT population.

Treatment group	Pretreatment N Mean (SD)	Month 0-12 N Mean (SD)	Month 12-24 N Mean (SD)
0.033	23 -0.7 (1.8)	24 2.5 (2.3)	24 1.0 (2.4)
0.067	24 -0.9 (2.8)	25 4.6 (3.1)	25 1.9 (2.6)
Untreated	16 -1.8 (1.9)	20 -0.8 (1.3)	20 -0.4 (0.8)
Primary analysis (Dunnett's test)*: 0.033 vs. untreated 0.067 vs. untreated Sec. analysis (Student's t-test): 0.067 vs. 0.033		p=0.0001 S p=0.0001 S p=0.0035	p=0.0300 NS p=0.0006 S p=0.1550

*The p-values in the table are not adjusted for multiple comparisons. The 'S' implies statistically significant even after correction for multiple comparisons, see also section 9.8.2.

Item 3: In Study TRN 90-079, Table 4 (volume 23/pg. 36) states that four patients had height velocity SDS at baseline >1. Below the table, the height velocity SDS values are given. (Patient 906:2 is said to be height SDS rather than height velocity SDS.) However, height velocity SDS, cm/year in Table 6 (volume 23/pg. 38), lists max values much higher than the values given on page 36 (Table 4). {Isn't cm/year wrong? Shouldn't height velocity SDS be dimensionless?} Looking at the data given on CD-ROM, there were nine values >1. Data agreed with Table 6 rather than Table 4.

Item 4: In Study TRN 90-080-8122-011 (Belgium), Table 4 (vol. 38/pg 36) indicates there are 3 patients whose pre-study HV SDS > 1 for chronological age. The first patient is in treatment group 0.1 (Pt. 06-24) with a value given as 1.4 SD. Table 6 on page 39 indicates there is a patient with a value of 1.8 in that group, not a value of 1.4. The data file lists patient 06-23 with a value of 1.78; patient 06-24 has a value of -0.16. How could a mistake in <u>both</u> patient number and value occur?

Table 4. Major protocol deviations.

Part A. 0-24 months	Treatment group	Number of patients	Patno.	Value of measurement
Prestudy HV SDS > + 1 for chronological age	0.1	1	06-24	1.4 SD
	0.067	1	03-17	1.4 SD
	Control	1	01-14	1.7 SD
Prestudy treatment with somatropin	0.1	1	06-23	-
Premature stop of somatropin treatment	0.067	1	01-19	-
Part B. Month 24 to 72				
Major deviation	Treatment group	Number of patients	Patno	
Prestudy HV SDS < + 1 for chronological age	0.1/untreated	1	06-24	
	0.067/retreated	1	03-17	
Missing visit 72.	0.1/untreated	1	04-42	

Table 6. Demographics and other baseline characteristics. ITT/safety population 0-24.

		Treatment group		
		0.1 N=19	0.067 N=20	Untreated N=13
Male	n	9	11	6
	%	47	55	46
Female	n	10	9	7
	%	53	45	54
Age at baseline, yrs	n	19	20	13
	MEAN (SD)	5.1 (1.9)	5.4(2.1)	4.9(1.9)
	MIN-MAX			
Bone age	n	18	20	12
	MEAN (SD)	3.8 (2.0)	4.5 (2.2)	3.7 (1.9)
	MIN-MAX			
Weight	n	19	20	13
	MEAN (SD)	12.3 (3.0)	13.2 (4.0)	12.0 (2.7)
	MIN-MAX			
Height, cm	n	19	20	13
	MEAN (SD)	94.1 (11.7)	96.1 (11.6)	94.0 (10.6)
	MIN-MAX			
Height SDS	n	19	20	13
	MEAN (SD)	-3.7 (0.8)	-3.5 (0.8)	-3.4 (1.0)
	MIN-MAX			
Height SDS for boneage	n	18	20	12
	MEAN (SD)	-1.0 (2.4)	-2.1 (1.5)	-1.2 (2.1)
	MIN-MAX			
Height velocity, cm/yr	n	19	20	13
	MEAN (SD)	6.8 (1.8)	6.5 (1.8)	7.2 (2.7)
	MIN-MAX			
Height velocity SDS, cm/yr	n	19	20	13
	MEAN (SD)	-0.8 (1.2)	-0.9 (0.9)	-0.6 (1.0)
	MIN-MAX			
Parental adj. Height SDS	n	19	20	13
	MEAN (SD)	-2.7 (1.2)	-2.5 (1.3)	-1.8 (1.2)
	MIN-MAX			

Data File Values

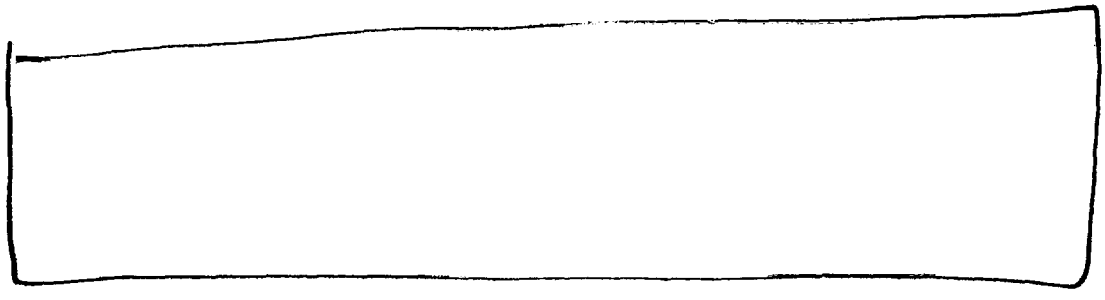
6	23	0	80006023	1.7833984889
6	23	12	80006023	2.8089296013
6	23	24	80006023	3.6353588144
6	24	0	80006024	-0.161323113

Item 5: In Study TRN 89-041 (page 36, volume 5), you state that there were three patients who had baseline height velocity SDS >1 (Pts. 0112, 0115, 0403). The data file indicates four patients. The patient not included in that summary is Pt. 1 from center 65 (Pt. 6501) with a baseline SDS of 2.14761. It is hard to imagine why this patient was not included if the person writing the summary is looking at the same data as in the datafiles.

Item 6: Please provide information on the patients who had missing values assigned for the primary efficacy variable in each study. You assigned 0 (if the 12th month value was missing) and -3 for the 24th month (if the 12th month was missing) for Genotropin patients. Did these patients have any other height velocity SDS values not at 12 and 24 months?

Document Preparation

Item 1:



Certification of direct translation of the forms should be acceptable, in the event that Pharmacia is unable to obtain translated, signed forms.

Item 2: Please ensure that all data appearing in tables match precisely when this data is discussed in the text.

Item 3: Please intensively quality assure and proof-read the study reports before resubmission. The original submission had far too many typographical, spelling, grammatical and English usage errors which impeded efficient and accurate review.

Item 4: Please insure that all volume references match (example given).

Volumes should NOT be re-numbered at the beginning of each section.

Item 5: At the time of resubmission, please provide 3 desk copies in MS WORD of the clin/stat section on CD-ROMs and 4 MS WORD CD-ROM desk copies of the labeling.

At the conclusion of the discussion, S. Malozowski noted that the Division would review the resubmission *de novo*, without prejudice. He noted that the Division encouraged the resubmission.

Although FDA minutes are the official documentation of the meeting, we note that Sponsor minutes have not been provided at this time; therefore, no discrepancies are noted.

Prepared by: _____, Regulatory Project Manager
Crystal King, P.D., M.G.A. date

Concurrence: _____, Meeting Facilitator
Robert Perlstein, M.D. date

Concurrences: Saul Malozowski, M.D., Ph.D., Medical Team Leader 11.19.00
James Gebert, Ph.D., Biopharmaceutics Reviewer 11.20.00

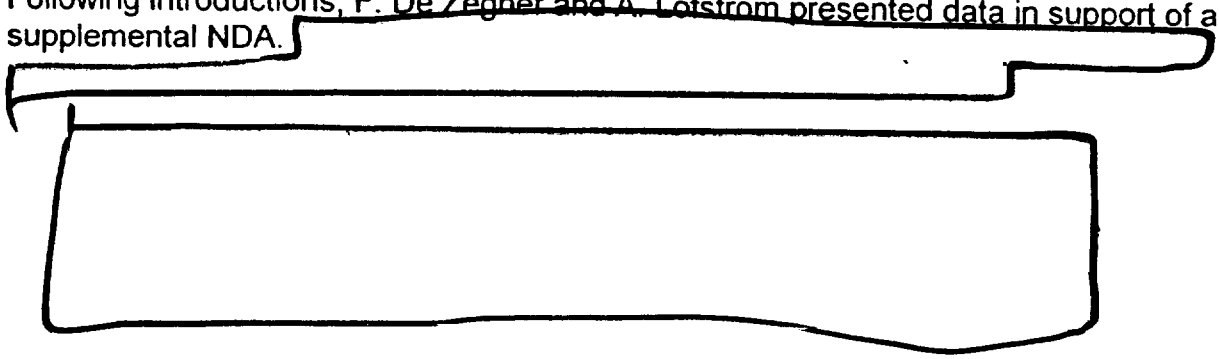
Meeting Minutes

NDA # and Drug Name:	20-280 Genotropin (somatropin [rDNA origin] for injection)
Meeting Date:	November 10, 1999
Time:	11:30 am
Location:	Parklawn "Potomac" Conference Room
Proposed Indication:	Long-term treatment of growth failure in pediatric patients who were born small for gestational age (SGA)
Sponsor:	Pharmacia & Upjohn Co.
Type of Meeting:	Guidance
Sponsor Contact:	Cindy Blanchard @ 616-833-6717
Regulatory Project Manager:	Crystal King @ 301-827-6423
FDA Participants:	Solomon Sobel, M.D., Division Director (internal meeting)
	Saul Malozowski, M.D., Ph.D., Medical Team Leader
	Robert Perlstein, M.D., Medical Reviewer
	Joy Mele, M.S., Biometrics Reviewer
	Crystal King, P.D., M.G.A., Regulatory Project Manager
Sponsor Participants:	Annika Lofstrom, Head of Clinical Operations, Global Medical Affairs, Peptide Hormones
	Francis de Zegher, M.D., Ph.D., Professor of Pediatrics, University of Leuven, Belgium
	Barbara Lippe, M.D., Senior Medical Director, Peptide Hormones, US
	Rolf Lundh, M.D., Ph.D., VP, Metabolic Diseases
	Cynthia Blanchard, Regulatory Manager, Global Regulatory Affairs

Meeting Objective: To discuss a supplemental application to use Genotropin for the long-term treatment of short children with persistent growth failure who were born small for gestational age (SGA).

Background: Genotropin was approved for growth failure due to growth hormone deficiency in August, 1997. Approval for use in childhood and adult onset growth hormone deficiency was granted in October, 1997.

Following introductions, F. De Zegher and A. Lofstrom presented data in support of a supplemental NDA.



Agenda Item 1: In the Phase 3 trials conducted by P&U, we have demonstrated significant catch-up growth in short children born SGA with persistent growth retardation who were treated with Genotropin for at least two years.

Is catch-up growth an acceptable primary efficacy variable that will allow registration for the treatment of this medical condition?

Agency Response:

- Yes

Additional areas discussed:

1) Differential diagnosis of SGA

2) Utilization of Genotropin in premature SGA infants

3) sNDA submission

   a) Statistical presentation and data format
   We will need to see all raw data, including data for patients who dropped out prior to study termination. The statistical presentation for each study should be separate; however, the study reports should be combined in the Integrated Summary of Efficacy. We would suggest a telecon with Statistics to discuss the data set format. Also, the Guidance document describes the electronic format. For safety, we will need large numbers of patients for evaluation.

   b) Inclusion criteria for each study
   We will need information on the inclusion criteria submitted: the criteria used for each study; the age of the children at therapy initiation; the rigorousness of the criteria.

c) Labeling
Regarding the labeling claim, B. Lippe noted that long-term treatment would be initiated after the age of two years in those children not demonstrating spontaneous catch-up growth.

d) Other
Please include the formulation and administration used for each study. Good records will be necessary for the clinical site audits; if discrepancies are noted, raw data will need to be supplied.

Although FDA minutes are the official documentation of the meeting, we acknowledge receipt of your meeting minutes submitted to the NDA on December 20, 1999.

Prepared by: /S/ 5/10/00, Regulatory Project Manager
Crystal King, P.D., M.G.A. date

Concurrence: /S/ 5/10/00, Meeting Facilitator
Saul Malozowski, M.D., Ph.D date

Concurrence: Robert Perlstein, M.D., Medical Reviewer 05.08.00
Joy Mele, M.S., Biometrics Reviewer 05.08.00

cc: NDA 20-280 /Division File
HFD-510: S.Malozowski/R.Perlstein/J.Mele/C.King