

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**19-676/S-016**

**Administrative Documents**

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

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ITEM 13

13. PATENT INFORMATION ON ANY PATENT WHICH CLAIMS THE DRUG

***21 U.S.C. 355 (b): The applicant shall file with the application the patent number and the expiration date of any patent which claims the drug for which the applicant submitted the application or which claims a method of using such drug and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner engaged in the manufacture, use or sale of the drug.***

Nutropin<sup>®</sup> [somatropin (rDNA origin) for injection] falls within the scope of the claims of Patent Number 5,096,885. This patent will expire on March 17, 2009. A copy of the patent is included in this section.

**NDA LABELING SUPPLEMENT (PUBERTAL DOSING):**

**ITEM 14**

**Nutropin<sup>®</sup> [somatropin (rDNA origin) for injection]**

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**14. PATENT CERTIFICATION WITH RESPECT TO ANY PATENT WHICH CLAIMS THE DRUG**

All investigations in this application were conducted by or for the applicant; hence, this section is not applicable.

### Exclusivity Checklist

NDA: <u>19-676-016</u>
Trade Name: <u>Nutropin</u>
Generic Name: <u>(Soma tropin [rDNA origin] for injection)</u>
Applicant Name: <u>Genentech, Inc.</u>
Division: <u>DMEDP, HFD-510</u>
Project Manager: <u>Crystal King</u>
Approval Date: <u>04/13/00</u>

**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	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
b. Is it an effectiveness supplement?	Yes	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>
c. If yes, what type? (SE1, SE2, etc.)	<u>SE-2</u>			
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	<input checked="" type="checkbox"/>	No	<input type="checkbox"/>

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.

Explanation:

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:

Explanation:

d. Did the applicant request exclusivity?	Yes	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
If the answer to (d) is "yes," how many years of exclusivity did the applicant request?				

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

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?	Yes	<input type="checkbox"/>	No	<input checked="" type="checkbox"/>
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If yes, NDA #

Drug Name:

**IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE**

<b>BLOCKS.</b>			
3. Is this drug product or indication a DESI upgrade?	Yes	No	<input checked="" type="checkbox"/>
<b>IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).</b>			
<b>PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES</b>			
(Answer either #1 or #2, as appropriate) <i>NOT APPLICABLE</i>			
1. Single active ingredient product.	Yes	No	
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).			
Drug Product			
NDA #			
Drug Product			
NDA #			
Drug Product			
NDA #			
2. Combination product.	Yes	No	
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 <u>any one</u> 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).			
Drug Product			
NDA #			
Drug Product			
NDA #			
Drug Product			
NDA #			

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

**PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS**

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."

<p>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.</p>	<p>Yes</p>	<p><input checked="" type="checkbox"/></p>	<p>No</p>	
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**IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.**

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.

<p>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?</p>	<p>Yes</p>	<p><input checked="" type="checkbox"/></p>	<p>No</p>	
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If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCKS.**

Basis for conclusion:

<p>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?</p>	<p>Yes</p>		<p>No</p>	<p><input checked="" type="checkbox"/></p>
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<p>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.</p>	<p>Yes</p>		<p>No</p>	
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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	<input checked="" type="checkbox"/>
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 #: <u>M 0380g</u>		IND #. <u>                    </u>			
Investigation #2, Study #:					
Investigation #3, Study #:					
3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.					
a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")					
Investigation #1		Yes		No	<input checked="" type="checkbox"/>
Investigation #2		Yes		No	
Investigation #3		Yes		No	
If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:					
Investigation #1 -- NDA Number					
Investigation #2 -- NDA Number					
Investigation #3 -- NDA Number					
b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?					
Investigation #1		Yes		No	<input checked="" type="checkbox"/>
Investigation #2		Yes		No	
Investigation #3		Yes		No	
If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:					
Investigation #1 -- NDA Number					
Investigation #2 -- NDA Number					
Investigation #3 -- NDA Number					
If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):					
Investigation #1 <u>M 0380g</u>		IND # <u>                    </u>			

Investigation #2			
Investigation #3			
<p>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.</p>			
<p>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?</p>			
Investigation #1		Yes	<input checked="" type="checkbox"/> No
IND#:			
Explain:			
Investigation #2		Yes	<input type="checkbox"/> No
IND#:			
Explain:			
Investigation #3		Yes	<input type="checkbox"/> No
IND#:			
Explain:			
<p>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?</p>			
Investigation #1		Yes	<input type="checkbox"/> No
IND#:			
Explain:			
Investigation #2		Yes	<input type="checkbox"/> No
IND#:			
Explain:			
Investigation #3		Yes	<input type="checkbox"/> No
IND#:			
Explain:			
<p>c. Notwithstanding an answer of "yes" to (a) or (b), are there</p>			

<p>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.)</p>	Yes		No	✓
<p>If yes, explain:</p>				



*ISI*  
 Signature of PM/CSO  
 Date: *3/22/00*

*ISI* *4/13/00*  
 Signature of Division Director  
 Date:

cc:  
 Original NDA  
 Division File  
 HFD-93 Mary Ann Holovac



# PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

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

NDA # 19-676-016 Supplement # 016 Circle one: (SE1) **(SE2)** SE3 SE4 SE5 SE6  
Nutropin (somatropin [rDNA origin])  
Trade and generic names/dosage form: for injection Action: AP/AE/NA

Applicant Genentech Therapeutic Class growth hormone

Indication(s) previously approved (A) Pediatric patients: (1) long-term tx of growth hormone failure due to lack of adequate endogenous GH secretion; (2) Tx of growth failure associated w/ chronic renal insufficiency; (3) Tx of short stature of Turner's Syndrome;  
Pediatric information in labeling of approved indication(s) is adequate  inadequate   
Proposed indication in this application no change in indication; (B) Adult patients: replacement of endogenous GH in male who meet specified criteria.  
(C) prepare larger doses during adolescence

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

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

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

Neonates (Birth-1month)  Infants (1month-2yrs)  Children (2-12yrs)  Adolescents (12-16yrs)

1. PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.
2. PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS. Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.
3. PEDIATRIC STUDIES ARE NEEDED. There is potential for use in children, and further information is required to permit adequate labeling for this use.
- a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
  - b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
  - c. The applicant has committed to doing such studies as will be required.
    - (1) Studies are ongoing.
    - (2) Protocols were submitted and approved.
    - (3) Protocols were submitted and are under review.
    - (4) If no protocol has been submitted, attach memo describing status of discussions.
  - d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.
4. PEDIATRIC STUDIES ARE NOT NEEDED. The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.
5. If none of the above apply, attach an explanation, as necessary.

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

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

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

Signature of Preparer and Title JSI

Date 3/24/00

Orig NDA/BLA # 19-676-016  
HFD 570 Div File  
NDA/BLA Action Package  
HFD-006/ KRoberts

(revised 10/20/97)

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

**16. DEBARMENT CERTIFICATION**

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

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

Signed by:

*Robert L. Gamick*

Robert L. Gamick, Ph.D

Title:

Vice President, Regulatory Affairs

Date:

*2/10/91*

MEMORANDUM

DATE: — April 11, 2000

FROM: John K. Jenkins, M.D.  
Acting Director, Division of ~~Product~~  
Products  
Director, Office of Drug Evaluation II

TO: NDA 19-676  
NDA 20-522

SUBJECT: Overview of supplemental NDA review issues

15/11/00

4/11/00

Endocrine Drug

Administrative

Supplement 016 was submitted by Genentech to the approved NDA 19-676 for Nutropin (somatotropin [rDNA origin] for injection) on June 11, 1999. This supplemental application was assigned a standard review. The 10-month user fee goal date for this application is April 14, 2000. A companion supplement (013) was submitted to NDA 20-522 for Nutropin AQ that cross references the Nutropin supplement and has an 10-month user fee goal date of April 28, 2000.

Clinical/Statistical

This supplemental NDA application proposes the addition of a higher dose of Nutropin (0.7 mg/kg/week versus the standard 0.3 mg/kg/week) for pubertal patients with growth hormone deficiency. In support of this new indication, the sponsor submitted the results of one open-label, randomized, multi-center trial in patients with growth hormone deficiency who were previously receiving the standard dose of GH and were in the early stages of puberty. Please refer to the medical review prepared by Dr. Perlstein and the statistical review prepared by Dr. Wang for details of this study and its results. Overall this study demonstrated that patients receiving the higher dose of GH had a significantly higher last measured height than those patients who continued to receive the standard dose of GH during puberty after a mean of 2.7 years of therapy. This increase in height was accomplished without a significant or worrisome increase in adverse effects of GH. An interesting observation was that patients who had a SD height score greater than -1.0 at baseline were able to attain normal adult heights with the standard dose regimen (mean SD height score at near-adult height = -0.1). This observation should be included in the labeling to avoid over dosing such patients in clinical practice with GH. Overall the study results support a conclusion that the higher dose regimen is effective in achieving greater height in GH deficient patients during puberty than the standard regimen. Information is lacking regarding the dose response for GH in these patients; however, given the long-term nature of the studies to evaluate this endpoint and the safety of the higher dose regimen in the current study, requirements for additional dose-ranging studies do not appear warranted.

This supplemental application is approvable pending agreement on adequate labeling with the sponsor.

Pharmacology/Toxicology

The sponsor did not submit any new animal studies in support of this new indication and none are required.

Chemistry, Manufacturing, and Controls

The new dosage does not involve any changes in the drug product or manufacturing procedures.

Data Integrity

No audits of the pivotal clinical study were requested from the Division of Scientific Investigations due to the small numbers of patients enrolled at each study site and the well established efficacy of GH in treatment of GH deficient children.

Labeling

There are several remaining minor issues related to the presentation of the data from the high-dose study in the labeling that remain to be negotiated with the sponsor.

Recommendation

This supplemental application, and its companion supplement for Nutropin AQ (NDA 20-522/S013, should be APPROVED once adequate labeling text is agreed with the sponsor. The sponsor will be reminded in the approval letter of their phase 4 commitments to highlight adverse reactions that occur in patients receiving the high dose regimen in their annual report, their periodic reports, and any expedited reports.

cc:

HFD-510/Division File  
HFD-510/Jenkins  
HFD-510/King



## Memorandum

Date: 3/26/00

From: Saul Malozowski  
— Medical Team Leader

Subject: Nutropin, NDA <sup>19676</sup>~~20986~~-S016. Pubertal Dose Study. Team leader recommendations

To: John Jenkins  
Acting Division Director, DMEDP

I have been intimately involved in the review of this NDA with the medical reviewer and the statistical team. I concur with their recommendations to approve this supplement. We are currently negotiating some wording modification to the label. The sponsor has already sent a draft proposal for a phase 4 commitment that is acceptable.

**Conclusion:**

I recommend approval of this product pending modifications to the submitted label in order to properly reflect the findings of the studies.

APPEARS THIS WAY  
ON ORIGINAL

# Memo

To: NDA 19-676, Supplement #16  
From: Robert S. Perlstein MD, Medical Officer  
CC: Saul Malozowski MD, Team Leader  
Crystal King, Project Manager  
Date: 3/29/2000  
Re: Amendment to Review of Study M0380g

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The purpose of this amendment is to comment further on which baseline characteristics of pubertal children with growth hormone deficiency (GHD) impact the response to therapy in the high and standard dose groups. As stated in my primary review, based on subgroup analyses (requested from and supplied by the sponsor subsequent to the original NDA submission) utilizing mean height standard deviation score (SDS) at near adult height as the primary outcome measure, GHD patients whose baseline height SDS were close to normal ( $>-1$ ) did not require a larger dose of recombinant human growth hormone (rhGH) during puberty to attain a satisfactory adult height. On the other hand, female gender and older age at baseline did not preclude a benefit from the larger dose of rhGH.

Subsequently, analyses performed by the Agency's statistical reviewer (not available prior to completion of my review) were brought to the attention of myself and my team leader by the statistical reviewer during labeling meetings. Utilizing mean last measured height adjusted for baseline height as the primary outcome measure, female subjects did not benefit significantly from the larger dose of rhGH, and in fact female subjects who were older at baseline grew less after treatment with the larger amount of rhGH (compared with the response observed in older females treated with the standard dose of rhGH). In contrast, male subjects of all ages appeared to benefit from the larger dose of rhGH. These results must be interpreted cautiously in view

of the small number of females participating in this study (7 in each dose group). Nonetheless, it was decided to present the results of this trial by gender in the label.

151  
MD 3/24/2000  
Robert Perlstein MD, FACP, FACE  
Medical Officer

151  
3/30/00  
Saul Malozowski MD, PhD  
Team Leader

CC: Original NDA 19-676; HFD-510 NDA 19-676  
Original IND  HFD-510 IND   
HFD-510 RPerlstein, SMalozowski, CKing

**RECORD OF TELEPHONE  
CONVERSATION/MEETING**

**Date: April 27, 1999**

Genentech is working on a labeling supplement for pubertal dosing for Nutropin. This t-con was held to discuss the planned supplement consisting of the completed interim report to be included and the revised package insert. The sponsor plans to do a complete electronic submission within the next several weeks.

K. Attie proposed that the interim report be submitted now, with final data to be submitted in a safety submission, approximately four months behind the submission.

Currently, about 80% have completed the protocol, having fused bones and no growth for one year. About 19 patients are still active and will take several years to meet adult height.

S. Malozowski requested that the statistical section clearly delineate the protocol findings vs. the additional analyses performed.

K. Attie noted that they do not have a pediatric insufficiency description for the package insert and will forward the draft paragraph.

**ACTION:** C.King to research the permissibility of delay of the Financial Disclosure information until 3 to 4 weeks following the submission.

**ADDENDUM:** Omission of required Financial Disclosure information is a Refusal to File issue. However, E. Galliers confirmed that as long as the information was in hand prior to the filing meeting, the Division would permit the delay.

151  
6/9/99  
\_\_\_\_\_  
Saul Malozowski, M.D., Ph.D., Medical Team Leader  
(Acting)

151  
\_\_\_\_\_  
Crystal King, Ph.D., M.G.A., Regulatory Project  
Manager

**NDA#: 19-676**

**Telecon/Meeting  
initiated by:**

Applicant/Sponsor  
 FDA  
**By: Telephone**

**Product Name:**  
Nutropin

**Firm Name:**  
Genentech

**Name and Title of Person  
with whom conversation  
was held:**

Ken Attie, M.D.  
Shawn McLaughlin,  
Regulatory Affairs

**Phone: 650-225-1915**

cc: NDA 19-676  
Division File  
HFD-510: SMalozowski/CKing



OFFICES OF DRUG EVALUATION  
ORIGINAL NDA/NDA EFFICACY SUPPLEMENT  
ACTION PACKAGE CHECKLIST

NDA 19-676/SE2-016 Drug: Nutropin

Applicant: Genentech, Inc. Chem/Ther/other Types: S

CSO/PM: Crystal King Phone: 827-6423 MailCode: HFD-510

ACTION PERF. GOAL DATE: <sup>UF10 =</sup> 4/14/00 DATE CKLIST CMLPTD: \_\_\_\_\_

Arrange package in the following order (include a completed copy of this CHECKLIST): \_\_\_\_\_ Check or Comment \_\_\_\_\_

1. ACTION LETTER with supervisory signatures  
Are there any Phase 4 commitments? AP  AE \_\_\_\_\_ NA \_\_\_\_\_  
Yes  No \_\_\_\_\_
2. Have all disciplines completed their reviews?  
if no, what review(s) is/are still pending? Yes  No \_\_\_\_\_
3. LABELING (package insert and carton and container labels).  
(if final or revised draft, include copy of previous version with ODE's  
comments and state where in action package the Division's review  
is located. If Rx-to-OTC switch, include current Rx Package insert  
and HFD-312 and HFD-560 reviews of OTC labeling.) Draft   
Revised Draft \_\_\_\_\_  
Final \_\_\_\_\_
4. PATENT INFORMATION
5. EXCLUSIVITY CHECKLIST
6. PEDIATRIC PAGE
7. DEBARMENT CERTIFICATION (Copy of applicant's certification for all NDAs submitted on or after June 1, 1992).
8. Statement on status of DSI's AUDIT OF PIVOTAL CLINICAL STUDIES NN  
If AE or AP ltr, explain if not satisfactorily completed. Attach a COMIS printout of DSI status.  
If no audits were requested, include a memo explaining why.

9. REVIEWS & MEMORANDA:

- |   |                                 |   |
|---|---------------------------------|---|
| DIVISION DIRECTOR'S MEMO  | If more than 1 review for any   | <input checked="" type="checkbox"/>                               |
| GROUP LEADER'S MEMO   | 1 discipline, separate reviews  | <input checked="" type="checkbox"/>                               |
| MEDICAL REVIEW  | with a sheet of colored paper.  | <input checked="" type="checkbox"/>                               |
| SAFETY UPDATE REVIEW  | Any conflicts between reviews   | <input checked="" type="checkbox"/>                               |
| STATISTICAL REVIEW  | must have resolution documented | <input checked="" type="checkbox"/>                               |
| BIOPHARMACEUTICS REVIEW   |                                 | <u>N/A - memo</u>   |
| PHARMACOLOGY REVIEW (Include pertinent IND reviews)             |                                 | <u>NN - memo</u>  |
| Statistical Review of Carcinogenicity Study(ies)                |                                 | <u>N/A</u>  |
| CAC Report/Minutes  |                                 | <u>N/A</u>  |
| CHEMISTRY REVIEW  |                                 | <u>10/6/97</u>  |
| Labeling and Nomenclature Committee Review Memorandum           |                                 | <u>N/A</u>  |
| Date EER completed _____ (attach signed form or CIRTS printout) | <u>N/A</u>                      | OK <input type="checkbox"/> No <input type="checkbox"/>           |
| FUR needed _____ FUR requested _____                            |                                 |   |
| Have the methods been validated? <u>N/A</u>                     |                                 | Yes (attach) <input type="checkbox"/> No <input type="checkbox"/> |
| Environmental Assessment Review / FONSI                         |                                 | Review <u>NN</u> FONSI <input type="checkbox"/>                   |

MICROBIOLOGY REVIEW NN  
What is the status of the monograph? \_\_\_\_\_

10. CORRESPONDENCE, MEMORANDA OF TELECONS, and FAXes
11. MINUTES OF MEETINGS   
Date of End-of-Phase 2 Meeting \_\_\_\_\_  
Date of pre-NDA Meeting 4/2/99 E-Com IND # [redacted]

12. ADVISORY COMMITTEE MEETING MINUTES N/A  
or, if not available, 48-Hour Info Alert or pertinent section of transcript. Minutes \_\_\_\_\_ Info Alert \_\_\_\_\_  
Transcript  No mtg

13. FEDERAL REGISTER NOTICES; OTC or DESI DOCUMENTS NN

14. If approval letter, has ADVERTISING MATERIAL been reviewed? Yes \_\_\_\_\_ No \_\_\_\_\_  
If no and this is an AP with draft labeling letter, has  
advertising material already been requested? Yes, documentation attached \_\_\_\_\_  
No, included in AP ltr

15. INTEGRATED SUMMARY OF EFFECTIVENESS (from NDA)

**ACTION PACKAGE CHECKLIST**

- Page 2 -

16. INTEGRATED SUMMARY OF SAFETY (from NDA)

\_\_\_\_\_ ✓

17. FDA LETTERS  
& MEMOS

\_\_\_\_\_ ✓

18. APPLICANT'S  
LETTERS

\_\_\_\_\_ ✓

19. CHARGE AND  
HISTORY CARD

\_\_\_\_\_ ✓

revision:1/16/98

# Memo

**To:** The File  
**From:** Crystal King, Regulatory Project Manager  
**Date:** 04/12/00  
**Re:** Pubertal Dosing Supplement Labeling

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We have agreed upon and accepted the draft labeling as submitted by Genentech on April 10, 2000.

*JSI*  
\_\_\_\_\_  
Sue-Jane Wang  
Biometrics Reviewer

*JSI* *(M)*  
\_\_\_\_\_  
Robert Perstein, M.D.  
Medical Reviewer

cc: NDA 19-656/S-016  
NDA 20-522/S-013  
Division Files  
HFD-510 R. Perstein/S.Wang/C.King

**DSI**

**NOT NEEDED**

Printed by Crystal King  
**Electronic Mail Message**

**Subject:** COMPANY CONFIDENTIAL

**Date:** 27-Oct-1999 09:27am  
**From:** Saul Malozowski  
MALOZOWSKIS  
**Dept:** HFD-510 PKLN 14B32  
**Tel No:** 301-827-6398 FAX 301-443-9282

**TO:** Crystal King ( KINGC )

**CC:** Robert Perlstein ( PERLSTEINR )

**Subject:** DSI inspection: GH and adolescent dosing

We have determine not to ask for an inspection for this NDA because the number of patients per center is quite small and does not justify it. If concerns arise during the review about disbalances between centers we may change our minds.

Saul

## FILING MEETING MINUTES

7/27/99

Drug/Application: NDA 19-676/S-016 Genentech: Nutropin Pubertal Dosing  
NDA 20-522/S-013 Genentech: Nutropin AQ

### 1. Filing Discussion:

- Clinical – No issues per Rob Perlstein and Saul Malozowski.
  - Note: Higher dose appears to be associated with acromegalic-type events. This may be an approval/labeling issue.
- Pharmacology – No issues per Dave Hertig.
- Micro—Not needed
- Devices—Not needed
- Project Management – Financial Disclosure included.
- Chemistry – No issues per Bill Berlin (via attached e-mail).
- Biopharmaceutics—Not needed per Rob Shore see review dated 7/21/99
- Biostatistics – No issues per Joy Mele (screening table attached).
  - Note: Need to review upcoming 4-month safety update to ensure there is sufficient patient data to satisfy safety criteria.
- DSI –No filling issues per Roy Blay.

### 2. Priority or Standard Review schedule: ~~Priority~~ Standard

3. Clinical Audit sites (list): Roy Blay will ascertain the number of patients per site from the sponsor and will then contact Rob Perlstein to determine review site.
4. Advisory Committee Meeting: Yes No
5. Review Timelines/Review Goal Date (with labeling):
  - MS Project timelines for the entire project and for individual disciplines were distributed. The UF<sub>10</sub> for 19-676 s/016 is April 14, 2000, and April 28, 2000, for 20-522 s/013. Office level review is NOT required. *Each discipline agreed that all reviews, with labeling, would be signed and delivered to Crystal King on or before Monday, February 28, 2000.*

NOTE: This supplement is available in the electronic document room.

**ACCEPTED FOR FILING**

Crystal King, Regulatory Project Manager  
/S/ 7/27/99

Saúl Malozowski, Medical Team Leader  
/S/

Attachments:

- (1) e-mail from William Berlin dated 7/27/99
- (2) 45-day screening by J. Mele

cc: NDA 19-676 s/016  
NDA 20-522 s/013  
HFD-510: C.King/S.Malozowski/R.Perlstein/D.Hertig/R.Steigerwalt/W.Berlin/S.Moore  
R.Shore/H.Ahn/J.Mele/T.Sahlroot  
HFD-344 R.Blav

Printed by Crystal King  
**Electronic Mail Message**

Activity: COMPANY CONFIDENTIAL

**Date:** 27-Jul-1999 09:49am  
**From:** William Berlin  
BERLINW  
**Dept:** HFD-510 PKLN 14B31  
**Tel No:** 301-827-6370 FAX 301-443-2356

**TO:** Crystal King ( KINGC )

**Subject:** Re: tickler

Crystal, it is 9:50, but there are still no filing issues for N  
19-676/S-016. I will have the review shortly.

b

APPEARS THIS WAY  
ON ORIGINAL

**45-Day Screening of NDA's  
Division of Biometrics II HFD-715**

**NDA #:** 19-676 SE2 -016

**Priority Classification:** probably non-priority

**Drug:** Nutropin (somatropin for injection)

**Sponsor:** Genentech, Inc.

**Number of Controlled Studies:**

**Indication:** treatment of growth failure due to lack of endogenous growth hormone

**Date of Submission:** June 11, 1999

**Date of 45-day Meeting:** July 27, 1999

**Statistical Reviewer:** Joy Mele, M.S. (HFD-715)

**Volume Numbers in Statistical Section:** Volumes 1-8

**Brief Summary of Controlled Clinical Trial**

<b>Study Number</b>	<b># of Sites</b>	<b>Design</b>	<b>Treatment Arms (N)</b>	<b>Duration of Treatment</b>
M0380	20 US	Open-label, randomized, ongoing of pubertal patients	0.3 mg/kg/wk (49) 0.7 mg/kg/wk (48)	Patients were followed until adult height (epiphyseal closure and no change in height for 12 months

**FILE-ABILITY CONCERNS**

ITEM (Section on pages 4-5 of the RTF Guidance document)	CHECK (NA if not applicable)
Index sufficient to locate necessary reports, tables, etc (1a)	Overall index not adequate – study report index good
Sufficient data listings and intermediate analysis tables to permit a statistical review (1c)	OK
Original protocols & subsequent amendments available in the NDA (1c)	YES
Endpoints and methods of analysis spelled out in the protocols and followed according to the study report (1c)	Protocol endpoint was adult height/ endpoint in study report is near-adult height. ANCOVA performed as described in the protocol
Interim analyses (if present) planned in the protocol and appropriate adjustments in significance level made (1c)	Study is ongoing so this could be considered an interim analysis
Intent-to-treat analyses performed (1c)	Yes on primary variable
Effects of dropouts on primary analyses investigated (1c)	An ITT analysis in addition to evaluable patients analysis was done
Designs utilized appropriate for the indications requested (2a+c)	OK
Sufficient patient exposure to evaluate safety (3c, ICH E1A for chronic LT trt -1,500 total, 300-600 for 6 months, 100 for 1 year)	???? – only 48 exposed to highest dose
Safety and efficacy for gender, racial, and geriatric subgroups investigated (3d)	It seems that no subgroup analyses were performed probably due to the small number of patients
Data analyses to support proposed dosing performed (3f)	Yes
Data from primary studies submitted on diskette or as part of CANDA	Yes – new SAS datasets requested

To: NDA 19-676, Supplement #16  
From: Robert S. Perlstein MD, Medical Officer  
CC: Saul Malozowski MD, Team Leader  
Crystal King, Project Manager  
Date: 03/24/00  
Re: Review of Safety Update

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The Safety Update for NDA 19-676, Supplement #16 was submitted on 19 November 1999 by the sponsor, Genentech, Inc. The Safety Update reported safety data for Study M0380g between 2 June 1998 and 14 September 1999. An analysis of this safety data can be found in the Medical Officer's NDA review, specifically in the review of Study M0380g in the Safety Results section (pages 44-52).

*/S/*  
*MD*  
Robert Perlstein MD, FACP, FACE  
Medical Officer

*/S/*  
*3/27/00*  
Saul Malozowski MD, PhD  
Team Leader

CC: Original NDA 19-676; HFD-510 NDA 19-676  
Original IND [redacted] HFD-510 IND [redacted]  
HFD-510 RPerlstein, SMalozowski, CKing

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**FEDERAL REGISTER NOTICES,  
OTC, OR DESI DOCUMENTS**

**NONE**

**ADVERTISING MATERIAL**

**Requested in Action Letter**

To: NDA 19-676, Supplement #16  
From: Robert S. Perlstein MD, Medical Officer  
CC: Saul Malozowski MD, Team Leader  
Crystal King, Project Manager  
Date: 03/24/00  
Re: Integrated Summary of Efficacy (ISE) and Integrated  
Summary of Safety (ISS)

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The ISE and the ISS can be found in the Efficacy and Safety Discussion, Conclusions, and Recommendations sections of the medical officer's review of Study M0380g (the only study included in the submission) on pages 53-65.

*RS/* *MD*  
Robert Perlstein MD, FACP, FACE  
Medical Officer

*RS/* *3/29/00*  
Saul Malozowski MD, PhD  
Team Leader

CC: Original NDA 19-676; HFD-510 NDA 19-676  
Original IND  HFD-510 IND   
HFD-510 RPerlstein, SMalozowski, CKing

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# CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

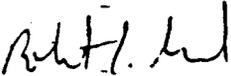
With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	See attachments	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Robert L. Garnick, Ph.D.	TITLE Vice President, Regulatory Affairs
FIRM/ORGANIZATION Genentech, Inc.	
SIGNATURE 	DATE 6/10/99

### Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services  
Food and Drug Administration  
5600 Fishers Lane, Room 14C-03  
Rockville, MD 20857

**Genentech, Inc.  
Protocol M0380g**

**List of PI's and Sub-I's for FDA Financial Disclosure**

<b>Principal Investigator Name and Address</b>	<b>Sub-Investigator Names</b>	<b>Financial Disclosure</b>
Gilbert P. August, MD Department of Endocrinology Children's Hospital National Med Center Washington, DC 20010		
Jennifer J. Bell, MD Columbia Presbyterian Medical Center Department of Pediatric Endocrinology, BHN-106 New York, NY 10032	None listed on 1572	
Dennis M. Bier, MD St. Louis Children's Hospital One Childrens Place St. Louis, MO 63110	None Listed on 1572	
Thomas Foley Jr., M.D. Children's Hospital of Pittsburgh Division of Endocrinology 3706 5 <sup>th</sup> Ave. at DeSoto Street Pittsburgh, PA 15213-3417		
Ronald Gotlin, MD The Children's Hospital 1056 E. 19 <sup>th</sup> Avenue Denver, CO 80218	None listed on 1572	
Madeline Harbison, MD New York Hospital - Cornell Med Center Dept of Pediatrics, Room N236 525 E. 68 <sup>th</sup> Street New York, NY 10021		
Raymond Hintz, MD Dept of Pediatrics, 8-322 Stanford University Medical Center Stanford, Ca 94305		
Abby Solomon Hollander, MD Washington University Med. Center St Louis Children's Hospital Campus Box 8116, One Children's Place St. Louis MO 63110	None listed on 1572	
Nancy J. Hopwood, MD Professor of Pediatrics University of Michigan Medical Center D3249 MPB, Box 0718 Ann Arbor, MI 48109-0718	None listed on 1572	
Nelly Mauras, MD Nemours Children's Clinic PO Box 5720 Jacksonville, FL 32247		
Margaret MacGillivray, MD Children's Hospital of Buffalo 219 Bryant St. Buffalo, NY 14222		

**Genentech, Inc.  
Protocol M0380g**

**List of PI's and Sub-I's for FDA Financial Disclosure**

Principal Investigator Name and Address	Sub-Investigator Names	Financial Disclosure
Wayne V. Moore, MD Children's Mercy Hospital Endocrine Department 2401 Gillham Road Kansas City, MO 64108	/	
Thomas Moshang, MD Dept of Endocrinology/Diabetes Children's Hospital of Philadelphia 34 <sup>th</sup> and Civic Center Blvd. Philadelphia, PA 19104	/	
Katrina L. Parker, MD Russell D. Cunningham, MD Assistant Professor of Pediatric Endocrinology 1600 Seventh Avenue South, ACC 608 Birmingham, AL 35233	/	
Leslie P. Plotnick, MD Department of Pediatric Endocrinology Johns Hopkins Hospital, CMSC 3-110 600 North Wolfe Street Baltimore, MD 21287-3311	None listed on 1572	
Edward O. Reiter, MD Department of Pediatrics Baystate Medical Center 759 Chestnut Street Springfield, MA 01199	/	
Alan Rogol, MD, PhD University of Virginia Health Sciences Center Department of Pediatrics, MR4-3037 Charlottesville, Va 22908	/	
Karen Rubin, MD University of Connecticut Health Center Department of Pediatrics, Building 12 Farmington, CT 06030	None listed on 1572	
William E. Russell, MD Vanderbilt University Medical Center Nashville, TN 37232-2579	/	
Paul Saenger, MD Montefiore Hospital, Division of Ped/Endo 111 E. 210 St. Bronx, NY 10467	None listed on 1572	
Dennis M. Styne, MD UC Davis MS-1A, Room 1134 Department of Pediatrics Davis, CA 95616	/	
Thomas Wilson, MD Department of Pediatrics SUNY Health Sciences Center, T-11 Stony Brook, NY 11794	/	

**Genentech, Inc.**  
**Protocol M0380g**  
**List of PI's and Sub-I's for FDA Financial Disclosure**

Principal Investigator Name and Address	Sub-Investigator Names	Financial Disclosure
David T. Wyatt, MD MACC Fund Research Center Dept. of Pediatrics 8701 Water Town Plank Road Milwaukee, WI 53226	/	

**ATTACHMENT**

Notes to Certification for Financial Interests of Clinical Investigators

Study M0380g

Questionnaire packages were sent via certified mail to all investigators and subinvestigators.

- 1) The following investigators/subinvestigators were unreachable because they are no longer at the study site:

— (sub)

— (sub)

Russell D. Cunningham (replaced by Katrina L. Parker)

— (sub)

— (sub)

— (sub)

— (sub)

- 2) No subjects were enrolled at Karen Rubin's site
- 3) No responses were received from the following subinvestigators at the time of submission, and following the sponsor's sending of a second letter via Federal Express.

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**ADVISORY COMMITTEE MEETING**

**NOT NEEDED**