CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020280/S008

PHARMACOLOGY REVIEW(S)

JUN 18 1997

18 Jun 97

NDA 20-280

Pharmacia and Upjohn Company
7000 Portage Road
Kalamazoo, MI 49001

Submission: dtd. 1 Nov 96

REVIEW AND EVALUATION OF PHARMACOLOGY AND TOXICOLOGY DATA
Supplemental Application (S-008) - Rec'd 4 Nov 96

Genotropin (somatropin [rDNA origin] for injection)

Recombinant (from E.coli) Human Growth Hormone

Indicated Use: [New Indication] Genotropin is indicated for long-term replacement therapy in adults with GHD of either childhood- or adult-onset etiology. GHD should be confirmed by an appropriate growth hormone stimulation test.

Manufacturer: Pharmacia AB, Sweden

Dosage: Adult GHD Patients. The recommended dosage at the start of therapy is not more than 0.04 mg/kg/week. The dose may be increased according to individual patient requirements to a maximum of 0.08 mg/kg/week, depending upon patient tolerance of treatment. It may be necessary to decrease the dose for patients who are older or obese.

Comments and Conclusion:

This Supplemental NDA consists primarily of new clinical information in support of the use of Genotropin for long-term replacement therapy in growth hormone deficient (GHD) adults of either childhood or adult-onset etiology with GH deficiency demonstrated in an appropriate GH stimulation test. Genotropin, recombinant human growth hormone (rhGH), is currently marketed for the long-term treatment of children who have growth failure due to an inadequate secretion of endogenous growth hormone (GH - NDA 20-280).

This submission contains no preclinical data but is referenced to the original NDA 20-280 for non-clinical pharmacology, toxicology, ADME-drug metabolism. No further preclinical studies are deemed necessary.

The Pharmacology portion of the Precautions section of the labeling is virtually the same as that of the currently marketed product.

/S/

David H. Hertig
Pharmacologist

NAI for pharmacology

/S/
6/18/97

cc: Original NDA 20-280,
HFD-345; HFD-510 NDA 20-280
HFD-510 RSteigerwalt, DHertig, MJohnston

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020280/S008

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

JUL 28 1997

NDA#: 20-280/SE1-008

APPLICANT: Pharmacia and UpJohn Company

NAME OF DRUG: Genotropin (somatropin [r DNA origin] for injection)

INDICATION: Long term replacement therapy in growth hormone deficient (GHD) adults.

DOCUMENTS REVIEWED: Volumes 20.1, 20.133-20.150, 20.215 of NDA 20-280/SE1-008, dated November 1, 1996

MEDICAL REVIEWER: This review has been discussed with the clinical reviewer, Saul N. Malozowski, M.D., HFD-510

RELEVANT ISSUES DISCUSSED IN THIS REVIEW

1. The sponsor's six double-blind, randomized , placebo-controlled studies taken together have established a statistical association between somatropin and the primary efficacy parameter (increase in lean body mass).

2. Statistical associations have also been established between somatropin and the incidence of arthralgia, stiffness of extremities, edema, pain in the extremities peripheral swelling, and paraesthesia.

3. The effect if any of somatropin on Quality of Life has not been established by these six studies.

KEY WORDS: arthralgia, body composition, bioelectrical impedance, dual x-ray absorptiometry, edema, extremities, growth hormone deficiency, lean body mass, paraesthesia, quality of life, stiffness, swelling, Wilcoxon

BACKGROUND

The sponsor has submitted six single-center, double-blind, randomized, placebo-controlled studies to support the use of Genotropin for long term replacement therapy in adults with growth hormone deficiency.

These studies had a similar design in that a six-month double-blind, placebo-controlled treatment period was followed by at least a six-month open-label treatment period in which all patients received Genotropin.

In each study, a starting dose of .125 IU/kg/week for four weeks was used, after which the dose was increased to .25 IU/kg/week subject to a maximum daily dose of 4 IU.

The primary objective of each study was to evaluate effects on body composition (lean body mass versus fat). Secondary objectives were to evaluate the change in Quality of Life and to study the safety of Genotropin.

The primary efficacy variable in each study was the intra-individual ratio (after/before) of lean body mass. The Wilcoxon Rank Sum Test was used to perform between-treatment comparisons due to the resulting distribution of the data.

Each study was a part of an international multiple independent trial (MIT) program. Data for each study was to be pooled for the evaluation of Quality of Life and safety.

At this point in time the results of a Quality of Life evaluation have not been provided by the sponsor.

Consequently, this review will focus on the primary efficacy variable (lean body mass) results as well as on the pooled safety (adverse experience) results.

The sponsor noted that many procedures have been developed over the years for the determination of body composition. Four procedures were used in the six primary clinical trails. The procedures used for each study are displayed in Table 1. These procedures are described in Volume 20.215 (pages 174-176) of the sponsor's submission.

A review of each of the above mentioned six studies follows.

STUDY TRN 91-081-01 (Sweden)

A total of 25 patients were enrolled and randomized (12 somatropin, 13 placebo) to receive six months of double-blind therapy.

Each randomized patient completed the six-month double-blind treatment phase of the study.

A total of 20 patients (11 somatropin, 9 placebo) experienced at least one adverse event during the six month double-blind treatment phase. In examining the adverse event data submitted by the sponsor, this reviewer noted that significantly more somatropin patients experienced peripheral swelling (6 somatropin, 0 placebo, p=.01) than did placebo patients. A statistical trend (p=.08) was also detected with regard to hypoaesthesia which was experienced by 4 somatropin patients but by no placebo patient.

As indicated in Table 1, body composition was determined by the BIA and four-compartment procedures. In each case, the sponsor did not detect a significant between-treatment difference with respect to the primary efficacy variable (BIA: p=11, four-compartment: p=.18).

The results of this reviewer's lean body mass BIA analyses which are in agreement with those of the sponsor are displayed in Table 2. In examining Table 2, one notes the lack of a statistically significant (p=.11) difference as somatropin patients experienced a median percent lean body mass increase of 1.4% compared to a corresponding placebo decrease of 1.3%.

Consequently, this study cannot stand alone in supporting a somatropin treatment effect with regard to the primary efficacy variable.

STUDY TRN 91-001 (Sweden)

A total of 20 patients were enrolled and randomized (10 somatropin, 10 placebo) to receive six months of double-blind therapy.

Each randomized patient completed the six-month double-blind treatment phase of the study.

In examining the adverse event data submitted by the sponsor, this reviewer noted that only somatropin patients (8, p<.001) experienced adverse events during the six-month double-blind treatment phase. Significantly more somatropin patients experienced arthralgia (7 somatropin, 0 placebo, p<.01) than did placebo patients.

As indicated in Table 1, body composition was determined by the BIA and DEXA procedures. In each case, the sponsor detected a significant between-treatment difference in favor of somatropin over placebo with respect to the primary efficacy variable (BIA: p=.04, DEXA: p<.01).

The results of this reviewers' lean body mass BIA analyses which are in agreement with those of the sponsor are displayed in Table 3. In examining Table 3, one notes that the somatropin patients significantly (p=.04) outperformed their placebo counterparts with regard to the primary efficacy variable as the median percent increases were 6.4% and 2.4% for the somatropin and placebo groups respectively.

STUDY TRN 91-081-02 (Sweden)

A total of 23 patients were enrolled and randomized (12 somatropin, 11 placebo) to receive six months of double-blind therapy. Two of these patients (both on somatropin) failed to complete the six-month double-blind treatment phase of the study. One patient was withdrawn by the investigator after 85 days due to the development of diabetes mellitus. The other patient decided to withdraw after 36 days due to edema and muscle-skeletal pain.

Eleven patients (10 somatropin, 1 placebo, p=.001) experienced at least one adverse event during the six-month double-blind treatment phase. In examining the adverse event data submitted by the sponsor, this reviewer noted that significantly more somatropin patients experienced edema or edema generalized (5 somatropin, 0 placebo, p=.047) than did placebo patients.

As indicated in Table 1, body composition was determined by four different procedures.

The sponsor's primary efficacy variable analyses yielded significant between-treatment differences in favor of somatropin over placebo with regard to the DEXA (p=.01), two-compartment potassium (p=.045), and four-compartment (p=.031) procedures. However statistical significance was not detected (p=.11) with regard to the BIA procedure. In each case, the sponsor excluded the 2 somatropin patients who withdrew prior to completing the six-month double-blind treatment phase.

The results of this reviewer's lean body mass BIA completers analyses which are in agreement with those of the sponsor are displayed in Table 4.

Table 4 also displays the results of this reviewer's all patient analyses which includes the 3 month BIA (last observation carried forward) measurements for the 2 somatropin patients who did not complete the six-month double-blind treatment phase. In this case there was no significant (p=.28) between-treatment difference with regard to the primary efficacy parameter. Last observation carry forward analyses could not be performed for the other 3 body composition measurement procedures as those measurements were only performed at baseline and at the six-month time point.

The clinical relevance of these findings in which three of the four body composition procedures support the lean body mass efficacy of somatropin should be assessed by the reviewing clinicians.

STUDY TRN 91-131-04 (U.K.)

A total of 32 patients were enrolled and randomized (14 somatropin, 18 placebo) to receive six months of double-blind therapy.

Three patients (2 somatropin, 1 placebo) failed to complete the six-month double-blind treatment phase of the study. One somatropin patient withdrew after 109 days due to peripheral edema, arthralgia, and headaches. The other somatropin patient withdrew after 78 days due to swelling

fingers and feet, and discomfort in both the knees and joints of hand. The placebo patient withdrew after 8 days due to extreme distress.

A total of 26 patients (11 somatropin, 15 placebo) experienced at least one adverse event during the six-month double-blind treatment phase. In examining the adverse event data submitted by the sponsor, this reviewer detected statistical trends (p=.06) with regard to the arthralgia as well as the paraesthesia incidence rate (4 somatropin, 0 placebo).

As indicated in Table 1, body composition was determined by the DEXA procedure.

The results of this reviewer's lean body mass DEXA analyses which are in agreement with those of the sponsor are displayed in Table 5. In examining Table 5, one notes that the somatropin patients significantly (p=.025) outperformed their placebo counterparts with regard to the primary efficacy variable. The somatropin group experienced a median percent increase of 3.9% in lean body mass compared to a .2% decrease in the placebo group.

STUDY TRN 91-131-08 (U.K.)

A total of 52 patients were enrolled and randomized (27 somatropin, 25 placebo) to receive six months of double-blind therapy.

Three somatropin patients failed to complete the six-month double-blind treatment phase of the study due to generalized muscle aches and pains, non-compliance, and carpal tunnel syndrome respectively.

A total of 37 patients (22 somatropin, 15 placebo, p=.09) experienced at least one adverse event during the six-month double-blind treatment phase.

In examining the adverse event data submitted by the sponsor, this reviewer noted that significantly (p=.03) more somatropin patients experienced pain in the extremities than did placebo patients (8 versus 1) during the six-month double-blind treatment phase.

As indicated in Table 1, body composition was determined by the DEXA procedure.

The results of this reviewer's lean body mass DEXA analyses which are in agreement with those of the sponsor are displayed in Table 6. In examining Table 6, one notes that the somatropin patients significantly (p=.01) outperformed their placebo counterparts with regard to the primary efficacy variable. The somatropin group experienced a median percent increase of 4.5% in lean body mass compared to a .4% decrease in the placebo group.

STUDY CTN 92-8124-011 (New Zealand)

A total of 20 patients were enrolled and randomized (10 somatropin, 10 placebo) to receive six months of double-blind therapy.

One placebo patient who felt uncomfortable with daily injections withdrew after 21 days of double-blind treatment. The remaining 19 patients completed the six-month double-blind treatment phase.

Sixteen (7 somatropin, 9 placebo) patients experienced at least one adverse event during the six-month double-blind treatment phase. In examining the adverse event data submitted by the sponsor, this reviewer noted a statistical trend (p=.09) in favor of placebo over somatropin with regard to the incidence of edema which was experienced by four somatropin patients (but not by any placebo patient) during the six-month double-blind treatment phase.

As indicated in Table 1, body composition was determined by the DEXA procedure.

The results of this reviewer's lean body mass DEXA analyses which are in agreement with those of the sponsor are displayed in Table 7. In examining Table 7, one notes the lack of a statistically significant (p=.49) difference as somatropin patients experienced a median percent lean body mass increase of 1.2% compared to a corresponding placebo decrease of 1.2%.

REVIEWER'S CONCLUDING COMMENTS

A total of 172 (85 somatropin, 87 placebo) patients were enrolled and randomized into the six double-blind, randomized, placebo-controlled studies which were discussed above.

Table 8 displays, the results of a pooled adverse event analyses which was conducted by this reviewer. Adverse events for which at least a statistical trend (p<.10) was detected between treatment groups are displayed. In examining this table, one notes a statistical association between somatropin and several adverse events. The clinical relevance of these associations, should be assessed by the reviewing clinicians.

Table 9 displays a summary of this reviewer's lean body mass analyses. BIA results are displayed for Studies TRN 91-001, TRN 91-081-01, and TRN 91-081-02 as this procedure was utilized in each of these studies. DEXA results are displayed for Studies 91-131-04, TRN 91-131-08, and CTN 92-8124-011 as this was the only procedure utilized in these studies.

In examining Table 9, one notes that statistical significance was achieved in favor of somatropin over placebo in Studies TRN 91-001 (p=.04), TRN 91-131-04 (p=.025) and TRN 91-131-08 (p=.01). Somatropin patients outperformed (but not significantly) their placebo counterparts in Studies TRN 91-081-01 (p=.11), TRN 91-081-02 (p=.11), and CTN 92-8124-011 (p=.49). However, the sponsor did detect significant differences in favor of somatropin over placebo in Study TRN 91-08-02 with

respect to the DEXA (p=.01), two-compartment potassium (p=.045) and four-compartment (p=.031) procedures.

In combining (Blocked Wilcoxon) the results for these studies, this reviewer detected a highly statistically significant difference in favor of somatropin over placebo with respect to the primary lean body mass efficacy parameter. Somatropin patients experienced a median percent increase of 3.2% compared to a .1% decrease by the placebo patients. These results are also displayed in Table 9.

REVIEWER'S OVERALL CONCLUSION

The six single-center, double-blind, randomized, placebo-controlled studies submitted by the sponsor, taken together have established a statistical association between somatropin and an increase in lean body mass in adults with growth hormone deficiency.

However data has not been submitted to support the sponsor's labeling statement that "treatment with Genotropin was also associated with positive effects on aspects of quality of life (energy, vitality, social isolation), as assessed by the Nottingham Health Profile questionnaire and the Physiological General Well-Being Index". The sponsor has been requested to submit Scientific Report 93 96 414 "Influence on Quality of Life of Somatropin (Genotropin) replacement therapy in growth hormone deficient adult patients, A Summary Report" in order that we may assess their above mentioned labeling statement.

In addition, the six studies have also established a statistical association between somatropin and the incidence of arthralgia, stiffness of extremities, edema, pain in the extremities, peripheral swelling, and paraesthesia.

/S/

APPEARS THIS WAY
ON ORIGINAL

Daniel N. Marticello
Mathematical Statistician

Concur: Dr. Nevius /S/ 7/28/97

Archival: NDA 20-280/SE1-008
HFD-510
HFD-510/SSobel,GTroendle,AFleming,SMalozowski,MJohnston
HFD-715/Division File,DMarticello,Chron

This review consists of 8 pages of text and 9 pages of tables

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ON ORIGINAL

TABLE 1

Body Composition Measurements+

Study	DEXA	BIA	Four	Two
TRN 91-001	X	X		
TRN 91-081-01		X	X	
TRN 91-081-02	X	X	X	X
TRN 91-131-04	X			
TRN 91-131-08	X			
CTN 92-8124-011	X			

+ DEXA: Dual x-ray absorptiometry

BIA: Two-compartment model with bioelectrical impedance analysis

Four: Four compartment model

Two: Two-compartment potassium model

TABLE 2

Study TRN 91-081-01

Lean Body Mass (kg)
BIA

	N	Baseline Median	Six Month Median	Median Intra-Individual Ratio
Placebo	13	63.6	64.5	.987
Somatropin	12	53.6	57.4	1.014
		p=.26		**p=.11**

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TABLE 3

Study TRN 91-001

Lean Body Mass (kg)
BIA

	N	Baseline Median	Six Month Median	Median Intra-Individual Ratio
Placebo	10	56.5	53.1	1.024
Somatropin	10	49.8	51.3	1.064
		p=.73		**p=.04**

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TABLE 4

Study TRN 91-081-02

Lean Body Mass (kg)
BIA

Completers

	N	Baseline Median	Six Month Median	Median Intra-Individual Ratio
Placebo	11	51.5	51.5	.992
Somatropin	10	54.5	58.7	1.031
		p=.97		**p=.11**

All Patients (LOCF)

	N	Baseline Median	Six Month Median	Median Intra-Individual Ratio
Placebo	11	51.5	51.5	.992
Somatropin	12	54.5	58.7	1.011
		p=.93		**p=.28**

TABLE 5

Study TRN 91-131-04

Lean Body Mass (kg)
DEXA

	N	Baseline Median	Six Month Median	Median Intra-Individual Ratio
Placebo	17	44.7	43.5	.998
Somatropin	12	44.0	45.4	1.039
		p=.67		**p=.025**

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TABLE 6

Study TRN 91-131-08

Lean Body Mass (kg)
DEXA

	N	Baseline Median	Six Month Median	Median Intra-Individual Ratio
Placebo	16	43.2	42.1	.996
Somatropin	17	57.5	59.0	1.045
		p=.18		**p=.01**

APPEARS THIS WAY
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TABLE 7

Study CTN 92-8124-011

Lean Body Mass (kg)
DEXA

	N	Baseline Median	Six Month Median	Median Intra-Individual Ratio
Placebo	9	47.8	47.8	.988
Somatropin	10	47.6	47.9	1.012
		p=.84		**p=.49**

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TABLE 8

Adverse Events+

Event	Somatropin (N=85)	Placebo (N=87)
Arthralgia	22 (25.9%)***	4 (4.6%)
Stiffness of Extremities	13 (15.3%)**	0
Edema	12++ (14.1%)**	0
Pain, extremities	16 (18.8%)*	4 (4.6%)
Swelling, peripheral	18 (21.2%)*	6 (6.9%)
Paraesthesia	11 (12.9%)*	2 (2.3%)
Fatigue	7 (8.2%)#	1 (1.1%)

\+ **Number of patients that experienced adverse events during the six-month double-blind treatment phase.**

++ **Edema peripheral (6), edema generalized (3), edema (3).**

p=.06

* **p<.01**

** **p<.001**

*** **p<.0001**

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TABLE 9

Lean Body Mass

Six Study Summary

Study		Median Intra-individual Ratio		
		Placebo	Somatropin	P-Value
TRN 91-001	(BIA)	1.024	1.064	.04
TRN 91-081-01	(BIA)	.987	1.014	.11
TRN 91-081-02	(BIA)	.992	1.031	.11
TRN 91-131-04	(DEXA)	.998	1.039	.025
TRN 91-131-08	(DEXA)	.996	1.045	.01
CTN 92-8124-011	(DEXA)	.988	1.012	.49
Pooled		**.999**	**1.032**	**<.00001**

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