CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020280/S008

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY & BIOPHARMACEUTICS REVIEW

NDA: 20-280/SE1-008	**SUBMISSION DATE (TYPE):**	**11/01/96** **03/13/97 (BB)** **04/30/97 (BB)**
BRAND NAME:	**Genotropin™**	
GENERIC NAME:	**somatropin [rDNA origin] for injection; rhGH**	
REVIEWER:	**Robert M. Shore, Pharm.D.**	
SPONSOR:	**Pharmacia & Upjohn,** **Kalamazoo, MI**	
TYPE OF SUBMISSION:	**Supplement - New or Modified Indication**	

OCT -9 1997

SYNOPSIS:

Genotropin™ (somatropin [rDNA origin] for injection;rhGH) is currently approved for the long-term treatment of pediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone. The sponsor is seeking an indication for long-term replacement therapy in adults with GHD of either childhood- or adult-onset etiology. Currently, there are 3 concentrations on the U.S. market: 4 IU/mL, 15 IU/mL, and 36 IU/mL. The 4 IU/mL is neither compositionally nor proportionally identical to the higher strengths; the 15 IU/mL and 36 IU/mL are compositionally similar but not proportional. Pharmacokinetic data in the original approved NDA indicated that the 4 IU/mL and 16 IU/mL formulations were not bioequivalent. There is no data on the bioequivalence of the 36 IU/mL formulation with the other formulations.

Four pharmacokinetic studies were submitted in this supplement. Overall, there is considerable variability in the pharmacokinetics of rhGH. Pharmacokinetic parameters are comparable between healthy adults, AGHD patients, and GHD children. The dose used in the pharmacokinetic studies (0.03 mg/kg) was larger than the highest dose proposed for use in adults (0.01 mg/kg/day). Bioavailability of the SC dose is similar between male and female AGHD patients. Intra-patient variability after repeated administration of rhGH was 15% for AUC_{0-t} and 45% for C_{max}. Two pilot studies demonstrated a lack of bioequivalence between the 4 IU/mL marketed formulation and developmental formulations (8 IU/mL and 32 IU/mL).

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II has reviewed (NDA) 20-280/SE1-008 submitted 11/01/96, 03/13/97, and 04/30/97. The overall Human Pharmacokinetic Section is acceptable to OCPB. Comments (p. 12) and labeling comments (p. 12) should be sent to the sponsor as appropriate.

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Table of Contents **Page**

SYNOPSIS 1
RECOMMENDATION 1
TERMS AND ABBREVIATIONS 3
BACKGROUND 3
PROTOCOL INDEX 4
DRUG FORMULATION 5
ANALYTICAL METHODOLOGY 5
HUMAN PHARMACOKINETICS AND BIOAVAILABILITY STUDIES 7
Bioavailability/Bioequivalence 9
Pharmacokinetics 11
Pharmacokinetic/Pharmacodynamic Relationships 11
COMMENTS 12

To Be Sent to the Sponsor 12
LABELING COMMENTS 12
Appendix 1: Complete Draft Labeling 15
Appendix 2: Study Summaries 29
Appendix 3: Formulation/Batch Information 43
Appendix 4: Assay Performance 53

(Complete Appendices and/or Attachments are available from DPE-II upon request)

TERMS AND ABBREVIATIONS:

20kD hGH .... 20 kiloDalton variant of human growth hormone which lacks amino acid residues 32-46
AGHD ..... adult growth hormone deficiency
$AUC_{(a-b)}$ ..... area under the plasma drug concentration-time curve from time a to time b
AUMC ..... area under the first moment curve
CI ..... confidence interval
CL ..... plasma clearance
Cmax ..... highest observed drug concentration
CV ..... coefficient of variation
F ..... bioavailability of drug
GHRD ..... growth hormone receptor deficiency
hFSH ..... human follicle stimulating hormone
hGH ..... human growth hormone (22 kD)
hLH ..... human luteinizing hormone
hPL ..... human placental lactogen (chorionic somatomammotropin, hCS)
hPRL ..... human prolactin
hTSH ..... human thyroid stimulating hormone
IM ..... intramuscular
IU ..... international unit (for somatropin 3 IU is approximately 1 mg)
IV ..... intravenous
k ..... elimination rate constant (lambda, λ)
LOD ..... limit of detection
LOQ ..... limit of quantitation
MAT ..... mean absorption time
MRT ..... mean residence time
mU ..... milli-international unit (1/1000 if an international unit)
ND ..... not determined
OCPB ..... Office of Clinical Pharmacology and Biopharmaceutics
PD ..... pharmacodynamic
PK ..... pharmacokinetic
rhGH ..... recombinant human growth hormone (22 kD)
SC ..... subcutaneous
T1/2 ..... apparent terminal half-life in serum
Tmax ..... time at which highest observed drug concentration (Cmax) occurs
Vd ..... apparent volume of distribution
Vss ..... apparent volume of distribution at steady-state

BACKGROUND:

Genotropin™ (somatropin [rDNA origin] for injection) is a polypeptide hormone of recombinant DNA origin. It has 191 amino acid residues and a molecular weight of 22,124 daltons. The amino acid sequence of the product is identical to that of human growth hormone of pituitary origin (somatropin). Genotropin™ is synthesized in a strain of *Escherichia coli* that has been modified by the addition of the gene for human growth hormone. Genotropin™ is a sterile white lyophilized powder intended for subcutaneous injection.

Genotropin™ is currently approved for the long-term treatment of pediatric patients who have growth failure due to an inadequate secretion of endogenous growth hormone. With this efficacy supplement, the sponsor is seeking an indication for long-term replacement therapy in adults with GHD of either childhood- or adult-onset etiology.

The sponsor (formerly Kabi Pharmacia) previously conducted four Biopharmaceutics studies of Genotropin™ rhGH that were included in the original submission (05/15/92) of NDA 20-280. All four studies were conducted

in Sweden and three are briefly summarized below (some information is from the Division of Biopharmaceutics review dated 02/10/94). Study TRN 85-040 used IM dosing with a different formulation and will not be referred to in this review, as the only approved route of administration is SC.

Study TRN 84-025 established that the pharmacokinetic profiles of Genotropin™ rhGH and met-hGH (somatonorm or somatrem; identical to pituitary hGH except for an additional methionine residue at the N-terminal) are similar when both are supplied as 4 IU/mL formulations and injected subcutaneously in healthy adult male volunteers . Each had a bioavailability of approximately 80% when compared to intravenously administered rhGH.

Study TRN 90-053 examined the bioequivalence of the 4 IU/mL and 16 IU/mL Genotropin™ rhGH formulations given by subcutaneous injection to healthy adult male volunteers. The $AUC_{(0-\infty)}$ and C_{max} values were statistically significantly higher (35% and 32%, respectively) for the 16 IU/mL formulation than for the 4 IU/mL formulation. Although the initial reviewer requested that the sponsor submit confidence intervals, none could be found in the responses.

Study TRN 87-050 examined the bioequivalence of the 4 IU/mL and 16 IU/mL Genotropin™ rhGH formulations when given by subcutaneous injection to children with GH deficiency. The C_{max} and $AUC_{(0-\infty)}$ values were higher (29% and 17%, respectively) for the 16 IU/mL formulation than for the 4 IU/mL formulation, but these differences were not statistically significant. Although the initial reviewer requested that the sponsor submit confidence intervals, none could be found in the responses.

From TRN 90-053 and TRN 87-050, the sponsor concluded that the 4 IU/mL and 16 IU/mL formulations are not bioequivalent. The Biopharm review from 02/10/94 does suggest that the medical officer evaluate the two formulations for therapeutic equivalence. However, the approved labeling does not address the issue of interchanging these formulations.

This efficacy supplement, SE1-008, contains four studies to be reviewed by OCPB, all of which included a 4 IU/mL formulation comparable to the U.S. market formulation after reconstitution. There are 6 primary clinical studies conducted in Europe identified by the sponsor to support the proposed indication. All of these clinical studies used a 16 IU/mL formulation

Currently, for somatropin, 3 IU are equivalent to 1 mg. This was changed about 1992, from 2.6 IU/mg.

PROTOCOL INDEX

Protocol Number	Title	Page
CTN 93-0195-002	Bioavailability of subcutaneously injected Genotropin™ 4 IU in growth hormone deficient adults	p.30
CTN 93-0195-001	Intra-individual variation of absorption kinetics of subcutaneously injected Genotropin™ 4 IU in adult growth hormone deficient subjects	p. 33
TRN 90-051 (Pilot Study)	A bioequivalence study of two different formulations of Genotropin™; 4 IU and 32 IU	p. 37
TRN 90-052 (Pilot Study)	A bioequivalence study of two different formulations of Genotropin™; 4 IU and 8 IU	p. 40

DRUG FORMULATION:

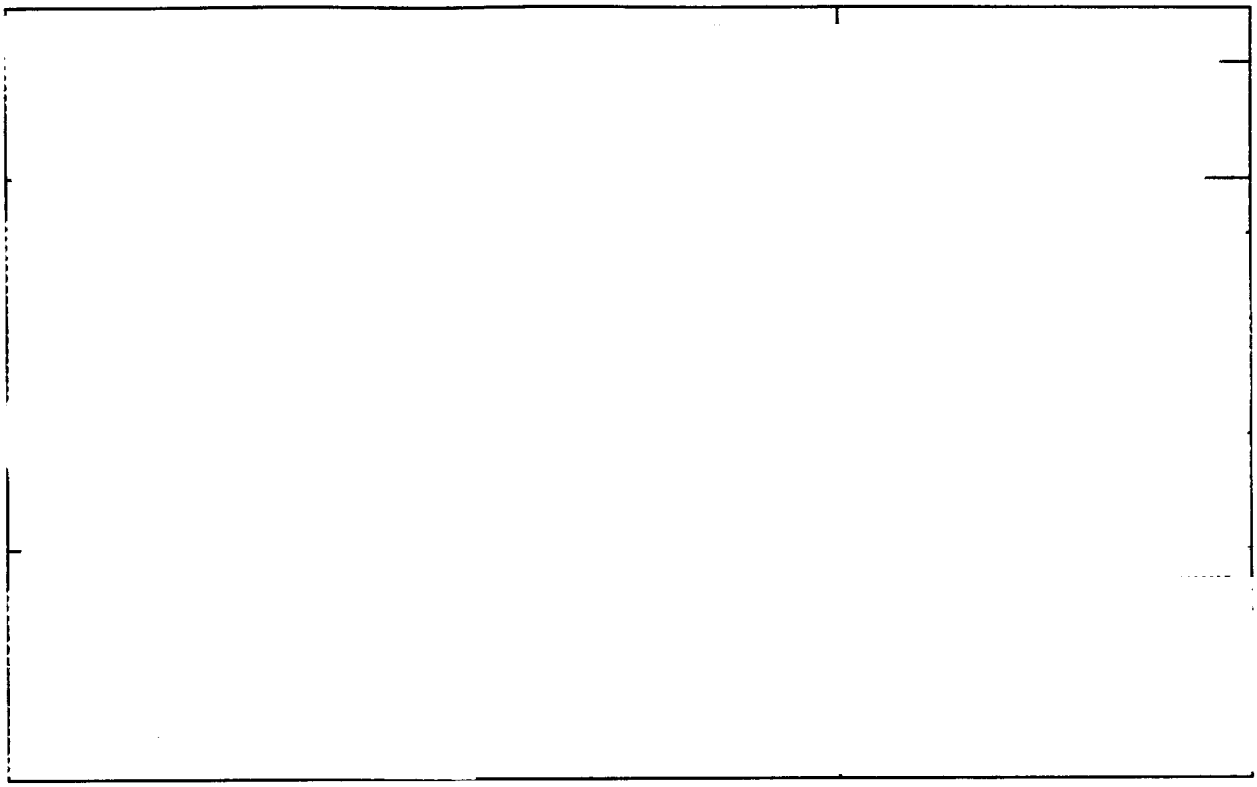
The 4 IU cartridge used in the CTN studies is the European market version, which is comparable to the 1.5 mg cartridge U.S. market version. The formulations are the same, both before and after reconstitution. The TRN studies used a formulation that is comparable to the after reconstitution, but the actual product consisted of two vials - one with lyophilized powder and the other with diluent. The 6 primary clinical trials conducted in Europe and submitted in this efficacy supplement used a 16 IU/mL cartridge formulation which is comparable to the U.S. 5.8 mg cartridge. The 8 IU and 32 IU developmental cartridge formulations are not currently marketed in the U.S. There is a 12 mg/mL cartridge and Pen12 unit recently approved (10/23/96) for the U.S. market; this formulation and device are not addressed in this submission. A bioequivalence waiver was submitted on 10/17/96 for this 12 mg/mL formulation, but was not reviewed by OCPB. However, the Chemist's review (dated 10/22/96) does state that in a verbal consultation with Biopharm and the Medical Officer, they indicated that "it is unlikely the increased concentration of rhGH in the formulation will affect the pharmacokinetics of the drug". Table 1 shows the different formulations. Batch information can be found in Appendix 3.

Table 1. Formulations after reconstitution

constituent	concentration per mL					
	1.5 mg cartridge	5.8 mg cartridge	16 IU cartridge (European)	12 mg cartridge	8 IU cartridge	32 IU cartridge
rhGH						
glycine						
mannitol						
sodium dihydrogen phosphate anhydrous						
disodium phosphate anhydrous						
M-cresol						

ANALYTICAL METHODOLOGY:

Table 2. Assay Parameters for GH



* See text for comments.

Table 3. Assay Parameters for GH

HUMAN PHARMACOKINETICS AND BIOAVAILABILITY STUDIES:

Table 4 summarizes the pharmacokinetic information generated in studies submitted in the approved NDA and Table 5 summarizes the pharmacokinetic data from this efficacy supplement. Studies which were submitted in support of this efficacy supplement are reviewed in the text.

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Table4. Summary of approved NDA mean PK data+

Study No.	Dose (IU/kg)	Conc (IU/mL)	Cmax (mU/L)	Tmax (hr)	t1/2 (hr)	$AUC_{(0-\infty)}$ (mU•hr/L)	Vd[a] (L)	CL[b] (L/min)	Fabs (%)
TRN 84-025	0.1 SC	4	53.3 <27>	5.2 <37>	2.0 <58>	513.5[c] <22>	43.0 <62>	0.20 <28>	77
(normal)	0.1 IV	4	ND	ND	0.4	668.8[c] <17>	7.2 <64>	0.20 <21>	-
TRN 87-050	0.1 SC	4	50.3	3.5	ND	317	ND	ND	-
(GHD)	0.1 SC	16	64.7	3.5	ND	370	ND	ND	-
TRN 90-053	0.1 SC	4	53.5 <53>	4.1 <27>	ND	285.4 <49>	ND	ND	-
(normal)	0.1 SC	16	70.9 <41>	4.0 <28>	ND	384.5 <31>	ND	ND	-

+ Reported as mean <CV%>
a Vd/F for SC; calculated as CL/k.
b CL/F for SC; calculated as Dose/$AUC_{(0-\infty)}$
c As per original NDA review, these values maybe overestimated due to the sampling schedule.

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Table 5. Summary of efficacy supplement PK data+

Study No.	Dose (IU/kg)	Conc (IU/mL)	Cmax (mU/L)	Tmax (hr)	t1/2 (hr)	$AUC_{(0-\infty)}$ (mU•hr/L)	Vd[b] (L)	CL[c] (L/min)	Fabs (%)
CTN 93-0195-002	0.1 SC	4	36.9[a] <46>	4.9	1.4 <38>	322.7* <41>	53.4 <77>	0.43 <56>	80.5
	0.05 IV	4	56.5[a] <36>	ND	ND	234.6* <37>	ND	0.33 <49>	-
CTN 93-0195-001	0.1 SC (first)	4	38.3[a] <80>	5.9 <28>	3.0 <48>	382.3[a] <37>	98.0[d,*] <65>	0.38[e] <37>	-
	0.1 SC (second)	4	37.5[a] <40>	6.6 <14>	2.2 <55>	385.3[a] <30>	72.9[d,*] <88>	0.36[e] <46>	-
TRN 90-051	0.1 SC	4	36.2 <53>	4.6 <32>	ND ND	303.5 <32>	ND ND	ND ND	- -
	0.1 SC	32	51.0[f] <37>	4.1 <29>	ND ND	396.6[f] <31>	ND ND	ND ND	- -
TRN 90-052	0.1 SC	4	31.5 <69>	5.7 <33>	ND ND	215.5 <50>	ND ND	ND ND	- -
	0.1 SC	8	28.3[g] <81>	5.1 <34>	ND ND	204.1[g] <59>	ND ND	ND ND	- -

+ Reported as mean <CV%>
a Baseline and dose-adjusted (0.1 IU/kg SC or 0.05 IU/kg IV).
b Vd/F for SC; calculated as CL/k.
c CL/F for SC; calculated as $Dose/AUC_{(0-\infty)}$.
d Reported incorrectly in the NDA.
e Reported as L•kg/hr in the NDA.
f Corrected for actual concentration of 29 IU/mL as per batch certificate
g Corrected for actual concentration of 7.4 IU/mL as per batch certificate
* calculated by reviewer.

I. Bioavailability/Bioequivalence

A. Absolute Bioavailability

The objectives of study CTN 93-0195-002 included the estimation of the absolute bioavailability of Genotropin™ rhGH given by subcutaneous administration and the investigation of the pharmacokinetics of rhGH after subcutaneous injection and intravenous infusion. The 4 IU/mL rhGH cartridge formulation was used.

Seventeen male and female patients with GH deficiency, aged and weighing participated in the study. However, only 15 of these patients were included in the pharmacokinetic calculations.

The study design consisted of an open-label subcutaneous injection of rhGH and an intravenous infusion of rhGH given in a randomized crossover sequence with an 8- to 41-day washout period between subcutaneous and intravenous administration. A single subcutaneous rhGH dose of 0.1 IU/kg was injected into the anterior upper lateral part of the right thigh of each patient. A single intravenous rhGH dose of 0.05 IU/kg was given as a 5-hour infusion to each patient. Serum profiles of GH were followed for 24 hours after the start of each rhGH administration. Serum GH concentrations were analyzed with the with

an LOQ of 0.1 mU/L. From the baseline-adjusted serum GH concentration versus time curves, the values of C_{max}, T_{max}, and $AUC_{(0-\infty)}$ were calculated (Table 5).

The SC injection of rhGH 0.1 IU/kg resulted in a mean C_{max} of 36.9 mU/L , and a mean T_{max} of 4.9 hr . The 5-hour intravenous infusion of rhGH 0.05 IU/kg resulted in a mean C_{max} of 56.5 mU/L

The reported mean±SD $AUC_{(0-\infty)}$/dose for GH resulting from rhGH subcutaneous injection was 48.1±18.8 mU·hr/L and intravenous rhGH infusion was 58.4±19.8 mU·hr/L. However, these parameters were generated by the sponsor; Table 5 includes AUC values, calculated by the reviewer, for comparison to other studies. The estimated bioavailability of rhGH resulting from SC administration was 80.5%, and the 95% confidence interval ranged from 70.5% to 92.1%. This estimate of absolute bioavailability was the same for both genders (80.6% for males [n=7] and 80.5% for females [n=8]). From these results it was concluded that the absolute bioavailability of Genotropin™ 4 IU given by SC administration to adults with GH deficiency is approximately 80%, and is comparable to that of healthy volunteers (Study TRN 84-025).

B. Bioequivalence

Two pilot studies (TRN 90-051 and TRN 90-052) were conducted to examine the bioequivalence between two concentrated formulations (8 IU/mL and 32 IU/mL) and the 4 IU/mL formulation. These two pilot studies were identical in design, with the only difference being the test formulation. Both were two period, randomized, crossover, open-label studies with SC injections of 0.1 IU/kg rhGH, one from the 4 IU/mL vial formulation and one from the test formulation. There was a 1-week washout period between injections. Each study enrolled 24 healthy male subjects. Serum profiles of GH were followed for 12 hours after each rhGH administration. Pharmacokinetic parameters are reported in Table 5. Bioequivalence was evaluated by determining the mean of the log(test/reference) for $AUC_{(0-\infty)}$ and C_{max} for the two formulations, generating the 90% CI, then back-transforming these parameters. The results are in Table 6. Neither the 8 IU/mL nor the 32 IU/mL demonstrated bioequivalence with the 4 IU/mL formulation, with the 8 IU/mL slightly less, and the 32 IU/mL more, bioavailable than the 4 IU/mL

Table 6. Back-transformed Mean Ln(Ratio) and 90% Confidence Intervals for GH parameters

Parameter*	Comparison	Lower Limit	Mean	Upper Limit
$AUC_{(0-\infty)}$	8/4		0.90	
	32/4		1.31	
C_{max}	8/4		0.89	
	32/4		1.54	

* AUC and Cmax values corrected for actual formulation concentrations as per batch certificates.

C. Intra-individual Variability

The objective of study CTN 93-0195-001 was to evaluate the intra-individual variation in the pharmacokinetics of GH after two SC administrations of the same cartridge formulation of Genotropin™ 4 IU, when administered to adult GH deficient subjects.

Seventeen subjects of both sexes with GH deficiency, aged received Genotropin™ 0.1 IU/kg body weight SC twice, with a wash-out period of 7-15 days between injections. Blood samples were drawn

over a period of 30 hours and assayed for serum concentrations of GH and IGF-1.

Table 5 reports the pharmacokinetic parameters. The observed C_{max} for serum GH was reached after about 6 hours The half-life for the declining phase was about 2.6 hours Clearance/F (Dose/AUC) values were calculated over the two periods to 0.37 L/min The apparent MRT was calculated as AUMC/AUC and was reported as 9.6 hours However, calculating MRT in this manner assumes an IV administration and fails to account for the MAT from the SC site of administration, thus giving a falsely large MRT (i.e., MRTtotal = MRTiv + MAT). The Vd values (MRTtotal•CL/F) generated from these MRT were, also falsely large (mean 212 L).

The intra-individual CV% for AUC_{0-t} and C_{max} was estimated to be 15% and 45%, respectively. When the study results were handled as if the two administrations would have been two different formulations, only the variable AUC_{0-t} demonstrated a 90% confidence interval within 0.80-1.25 (Table 7).

Table #. Back-transformed Mean Ln(Ratio) and 90% Confidence Intervals for GH Parameters

Parameter	Lower Limit	Mean	Upper Limit
$AUC_{(0-t)}$		1.04	
C_{max}		1.09	

The serum IGF-I profiles as response to the administered Genotropin™ were similar in period 1 and 2, in each individual; the intra-individual CV for AUC_{0-t} was estimated to be 19% . The maximum concentration observed was on the average 183 ng/mL No correlation between the pharmacokinetics of GH and the pharmacodynamic response of IGF-1 has been explored in this study. However, no data on the IGF-1 assay were submitted.

II. Pharmacokinetics

A. Dose Ranging

As noted in the submission, a study (TRN 87-077/89-020) using a starting dose of about 0.5 IU/kg/week (0.16 mg/kg/week) showed efficacy in AGHD patients, but the side-effect profile suggested that future studies be conducted at a lower dosage regimen. In this study, the mean dose at 12-18 months follow-up was 0.21 IU/kg/week (0.07 mg/kg/week).

The primary clinical studies used a dosage regimen of 0.125 IU/kg/week (0.04 mg/kg/week) for four weeks, after which the dose was increased to 0.25 IU/kg/week (0.08 mg/kg/week). The dose could be individualized in response to side effects.

III. Pharmacokinetic/Pharmacodynamic Relationships

The relationship between GH and IGF-1 was not explored in this submission.

COMMENTS:

LABELING COMMENTS:

The following labeling changes should be sent to the sponsor:

PHARMACOKINETICS
Absorption
Following a 0.03 mg/kg subcutaneous (SC) injection in the thigh of the 1.3 mg/mL GENOTROPIN to adult GHD patients, approximately 80% of the dose was systemically available as compared with that available following intravenous dosing. Results were comparable in both male and female patients. Similar bioavailability has been observed in healthy adult male subjects.

The AGHD data is from study CTN 93-0195-002 of the supplement.

In healthy adult males, following an SC injection in the thigh of 0.03 mg/kg, the extent of absorption (AUC) of a concentration of 5.3 mg/mL GENOTROPIN was 35% greater than that for 1.3 mg/mL GENOTROPIN. The mean (± standard deviation) peak (C_{max}) serum levels were 23.0 (± 9.4) ng/mL and 17.4 (± 9.2) ng/mL, respectively.

These data are from study TRN 90-053 in the approved NDA. As per the Biopharm review of that approved NDA, these Cmax values were 70.9 ± 28.9 mU/L for the 5.3 mg formulation and 53.5 ± 28.4 mU/L for the 1.3 mg formulation. Using 4 IU = 1.3 mg, this reviewer re-calculated the above values.

In a similar study involving pediatric GHD patients, 5.3 mg/mL GENOTROPIN yielded a mean AUC that was 17% greater than that for 1.3 mg/mL GENOTROPIN. The mean C_{max} levels were 21.0 ng/mL and 16.3 ng/mL, respectively.

These data are from study TRN 87-050 in the approved NDA. As per the Biopharm review of that approved NDA, these Cmax values were 64.7 mU/L for the 5.3 mg formulation and 50.3 mU/L for the 1.3 mg formulation. Using 4 IU = 1.3 mg, this reviewer re-calculated the above values.

Adult GHD patients received two single SC doses of 0.03 mg/kg of GENOTROPIN at a concentration of 1.3

mg/mL, with a one- to four-week washout period between injections. Mean C_{max} levels were 12.4 ng/mL (first injection) and 12.2 ng/mL (second injection), achieved at approximately six hours after dosing.

This data is from study CTN 93-0195-001 of the supplement. The reported mean Cmax values are 38.3 mU/L and 37.5 mU/L for the first and second injection, respectively. The above values were calculated using 4 IU = 1.3 mg.

There is no data on the bioequivalence between the 12 mg/mL formulation and either the 1.3 mg/mL or the 5.3 mg/mL formulations.

No *in vitro* nor *in vivo* data has been submitted that would address bioequivalence between the 12 mg/mL formulation and the two lower strength formulations.

Distribution
The mean volume of distribution of GENOTROPIN following administration to GHD adults was estimated to be 1.3 (± 0.8)

The volume calculation submitted in the supplement was incorrect (i.e., it assumed an IV bolus dose) and this reviewer re-calculated these values from the first period of study CTN 93-0195-001.

Metabolism
The metabolic fate of GENOTROPIN involves classical protein catabolism in both the liver and kidneys. In renal cells, at least a portion of the breakdown products are returned to the systemic circulation. The mean terminal half-life of intravenous GENOTROPIN in normal adults is 0.4 hours, whereas subcutaneously administered GENOTROPIN has a half-life of 3.0 hours in GHD adults. The observed difference is due to slow absorption from the subcutaneous injection site.

For the IV dose, the 0.4 hr is from study TRN 84-025 which included only normal adults. There were no calculations submitted for the half-life of the IV dose from study CTN 93-0195-002 in AGHD. For the SC half-life, the data is from the first period of study CTN 93-0195-001 in AGHD.

Excretion
The mean clearance of subcutaneously administered GENOTROPIN in 16 GHD adult patients was 0.3 (± 0.11) L/hrs/kg.

Special Populations
Pediatric: The pharmacokinetics of GENOTROPIN are similar in GHD pediatric and adult patients.

Gender: No gender studies have been performed in pediatric patients; however, in GHD adults, the absolute bioavailability of GENOTROPIN was similar in males and females.

Race: No studies have been conducted with GENOTROPIN to assess pharmacokinetic differences among races.

Renal or hepatic insufficiency: No studies have been conducted with GENOTROPIN in these patient populations.

Table 1
Mean SC pharmacokinetic parameters in adult GHD patients

	Bioavailability (%) (N = 15)	T_{max} (hours) (N = 16)	CL/F (L/hr x kg) (N = 16)	Vss/F (L/kg) (N = 16)	$T_{½}$ (hours) (N = 16)
Mean (± SD)	80.5 *	5.9 (± 1.65)	0.3 (± 0.11)	1.3 (± 0.80)	3.0 (± 1.44)
95% CI	70.5 - 92.1	5.0 - 6.7	0.2 - 0.4	0.9 - 1.8	2.2 - 3.7

T_{max} = time of maximum plasma concentration
CL/F = plasma clearance
Vss/F = volume of distribution
$T_{½}$ = terminal half-life
SD = standard deviation
CI = confidence interval

* The absolute bioavailability was estimated under the assumption that the log-transformed data follow a normal distribution. The mean and standard deviation of the log-transformed data were mean = 0.22 (± 0.241).

All parameters in Table 1 are from the first period of study CTN 93-0195-001 except for the bioavailability which is from study CTN 93-0195-002.

Robert M. Shore, Pharm.D.
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics
DATE

/S/ 10/09/97

RD initialed by Hae-Young Ahn, Ph.D., Team Leader 09/14/97

FT initialed by Hae-Young Ahn, Ph.D., Team Leader /S/ 10/9/97

cc: NDA 20-280/SE1-008 (orig., 1 copy), HFD-510(Malozowski, Johnston, Hertig, Berlin), HFD-340 (Vishwanathan), HFD-870(Shore, Ahn, M.Chen), CDR (Barbara Murphy).

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