

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-538

PHARMACOLOGY REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 21-538
SERIAL NUMBER: 000
DATE RECEIVED BY CENTER: May 9, 2006
PRODUCT: Accretropin™ (r-hGH, somatropin, —)
INTENDED CLINICAL POPULATION: — treatment of children with growth failure due to an inadequate secretion of normal endogenous growth hormone and treatment of short stature associated with turner syndrome in pediatric patients whose epiphyses are not closed. **b(4)**
SPONSOR: Cangene Corp., Ontario, Canada
DOCUMENTS REVIEWED: Pharmacology and Toxicology
REVIEW DIVISION: Division of Metabolism and Endocrinology Products
(HFD-510)
PHARM/TOX REVIEWER: Herman Rhee, Ph.D.
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PROJECT MANAGER: Kati Johnson

Date of review submission to Division File System (DFS): February 16, 2007

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EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: Approval

Pharmacology and toxicology recommends approval of NDA21-538

B. Recommendation for nonclinical studies: None

The following preclinical findings should be included in labeling instructions as indicated under "Pharmacology Recommendation Section", which is briefly summarized below.

C. Recommendations on labeling:

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies for carcinogenicity and impairment of fertility with Accretropin™ have not been performed.

Pregnancy

Pregnancy Category C — Animal reproduction studies have not been conducted with Accretropin™. It is not known whether Accretropin™ can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Somatropin should be given to a pregnant woman only if clearly needed.

Nursing Mothers

There have been no studies conducted with Accretropin™ in nursing mothers. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when somatropin is administered to a nursing woman.

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings

Drug Product Accretropin™ (recombinant human growth hormone (r-hGH); somatropin) is a protein produced by recombinant DNA technology. It is produced during fermentation in *E. coli* yielding a protein containing 192 amino acids. The N-terminal amino acid, methionine, is later removed to yield a protein that is chemically, immunologically and physicochemically identical to pituitary derived human growth hormone, consisting of 191 amino acids in a single polypeptide chain.

An acute single dose and subacute 10-day repeated dose subcutaneous injection toxicity study (study#88637) of _____ (Accretropin) were conducted in Sprague-Dawley CD (CrI:CD(SD)BR) rats. Five male and five female rats were administered _____ subcutaneously at dose of 0, 0.5 and 2.5 mg/kg/day once or for 10 days. There were no toxicologically significant differences between the control and treated groups following either a single dose or multiple doses of _____. There were no treatment-related gross pathological findings following either single or repeated administration and there were no treatment-related histopathological findings following 10-day repeat administration. **b(4)**

Ten Sprague-Dawley CD (CrI:CD(SD)BR) rats/sex/group were administered _____ subcutaneously at doses of 0, 0.5 and 2.5 mg/kg/day for 4 weeks. There were no deaths in all groups. There were no treatment-related effects on clinical observations, hematology, and blood chemistry. As expected, body weights, food consumption or organ weights were increased. There were no gross lesions and histopathological findings as a result of the treatment except for injection site lesions. Increased bodyweight gain in the HD treated animals (group 3) in the first week. **b(4)**

B. Pharmacologic activity

The sponsor performed a 10-day potency (weight gain) test of _____ (Accretropin) in hypophysectomized rats. Sixteen hypophysectomized male Sprague-Dawley CD (CrI:CD(SD)Br) rats were administered subcutaneously either _____ or Humatrope at doses of 0, 0.1, 0.5 and 1.0 mg/kg/day for 10 days. Both _____ and Humatrope increased absolute body weight so that the two growth hormone products have similar pharmacological effects. **b(4)**

Growth hormone receptors are widely distributed throughout the body. The receptor activation is initiated by the binding of a single molecule of hGH to two hGH receptors, to form a ligand-binding-site-occupied by the hormone. The bioassay using the rat weight gain assay is an integral part of the control and definition of potency of each batch of rhGH. It appears that limited toxicology studies with Accretropin™ indicated that its

general toxicology profiles are consistent with those of somatropin, based on the published literature.

Two studies were performed to demonstrate efficacy ———. Study GA-005/5A and study GA-007/7A were conducted in children with short stature who were diagnosed with GHD or Turner Syndrome, respectively. In these studies, height velocity in subjects treated ——— was compared to height velocity of age and gender matched standards for healthy children. Children with GHD were recruited in Poland and Hungary, and children with Turner Syndrome were recruited in Poland only. Both studies were conducted as single-arm, open-label, non-randomized, historically controlled long-term studies of 36 months duration. A historically controlled design was chosen because the inclusion of a placebo arm in a clinical study where gold standard treatments are available was not considered to be ethical.

b(4)

C. Nonclinical safety issues relevant to clinical use

None

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-538

Review number: 01

Sequence number/date/type of submission: 000/May 9, 2006/Commercial

Information to sponsor: Yes (x) No ()

Sponsor and/or agent: Cangene Corp., Massinssauga, Ontario, Canada Tel(905-673-0200)

Manufacturer for drug substance: Cangene, Corp., Winnipeg, Manitoba, Canada

Reviewer name: Herman Rhee, Ph.D.

Division name: Metabolism and Endocrine Product

HFD #: 510

Review completion date: 2/5/2007

Drug:

Trade name: Accretropin

Generic name: Somatropin

Code name: —

Chemical name: rH-Growth hormone

CAS registry number: NA

Molecular formula/molecular weight: $C_{990}H_{1528}N_{262}O_{300}S_7/22,125$ Daltons

b(4)

Structure: The primary structure is identical to natural, pituitary derived human GH and to Somatropin expressed in E. coli (Humatrope, Genotropin or Nutropin) or in mammalian cells (Saizen).

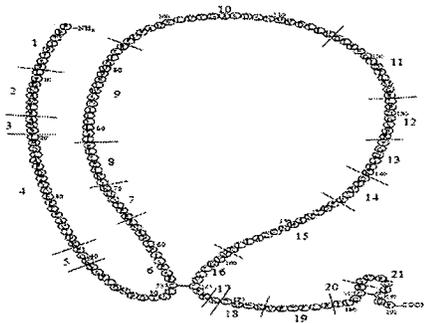


Figure 3.2.S.3.1-1: The primary structure of rhGH showing tryptic cleavages sites

Relevant INDs/NDAs/DMFs: (Humatrope), IND 71,344 (Nutropin), IND72,397(Norditropin), NDA20280(Genotropin), and NDA21905(Valtropin) IND62,147

b(4)

Drug class: recombinant human growth hormone

Intended clinical use and population:

Long-term treatment of pediatric patients who have growth failure due to an inadequate secretion of normal endogenous growth hormone. And treatment of short stature associated with Turner syndrome in pediatric patients whose epiphyses are not closed.

Clinical formulation:

Accretropin™ is distributed in a liquid solution containing 1 mL of a 5 mg/mL solution of growth hormone (15 IU/mL). The formulation also contains 0.75% NaCl, 0.34% Phenol (as preservative), and 0.2% Pluronic F-68 (a non-ionic surfactant) and is designed for subcutaneous administration. Accretropin™ is stabilized to pH 6.0 with 10 mM NaPO₄ buffer. Preclinical, clinical and commercial formulations are summarized in a table below. Pluronic F68 is a surfactant and the sponsor is going to use 0.2%, which is acceptable because it has been used in other marketed, approved products at this concentration. All other ingredients are GRAS.

Component	Preclinical/ Clinical		Commercial	
	Concentration (in a 1 mL fill vial)	Concentration (as mg/vial)	Concentration (in a 1 mL fill vial)	Concentration (as mg/vial)
Pluronic F68	0.2%	2 mg	0.2%	2 mg
Sodium phosphate,				
Sodium phosphate.				
Phenol			0.34%	3.4 mg
Sodium chloride	0.75%	7.5 mg	0.75%	7.5 mg
Recombinant human growth hormone (rhGH)	5 mg	5 mg	5 mg	5 mg

b(4)

† The resulting phosphate buffer is 10 mM with pH 6.0 ± 0.2.

†† The resulting phosphate buffer is 10 mM with pH 6.0 ± 0.3.

Route of administration: Subcutaneous injection

DOSAGE AND ADMINISTRATION

Accretropin™ [(somatropin) for injection] dosage and administration schedule should be individualized for each patient. Therapy should not be continued if epiphysial fusion has occurred. Response to growth hormone therapy tends to decrease with time. However, failure to increase growth rate, particularly during the first year of therapy, should prompt close assessment of compliance and evaluation of other causes of growth failure such as hypothyroidism, under-nutrition and advanced bone age.

In growth hormone deficient pediatrics, the weekly dosage is 0.18 mg/kg (0.54 IU/kg). The maximum weekly dose is 0.3 mg/kg (0.90 IU/kg). It can be divided into equal doses given on 3 alternate days, 6x/week or daily.

In Turner's patients, a weekly dosage is 0.375 mg/kg (1.125 IU/kg) by subcutaneous injections, which can be divided into equal daily or 3 alternate days dosing.

CONTRAINDICATIONS

Accretropin™ is contraindicated in patients with a known hypersensitivity to somatropin or any of its excipients. Based on clinical experience with other hGH products, the following are contraindications for Accretropin™:

Growth hormone should not be used for growth promotion in pediatric patients with closed epiphyses. Growth hormone should not be used or should be discontinued when there is any evidence of active malignancy. Anti-malignancy treatment must be complete with evidence of remission prior to the institution of therapy. Growth hormone should be discontinued if there is evidence of recurrent malignancy or neoplastic activity. Growth hormone is contraindicated in patients with proliferative or preproliferative diabetic retinopathy.

DRUG INTERACTIONS

Excessive glucocorticoid therapy may prevent optimal response to somatropin. If glucocorticoid replacement therapy is required, the glucocorticoid dosage and compliance should be monitored carefully to avoid either adrenal insufficiency or inhibition of growth promoting effects. There was no evidence, in the controlled studies involving Accretropin™, of interaction with drugs commonly used in the treatment of routine pediatric problems/illnesses. However, formal drug interaction studies have not been conducted.

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission:

1. An acute single dose and 10-day single dose subcutaneous toxicity study in rats
2. A 28-day repeated subcutaneous toxicity study in rats

Studies not reviewed within this submission:

None

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

Accretropin™ (recombinant human growth hormone (r-hGH); somatropin) is a protein produced by recombinant DNA technology. It is produced during fermentation in *E. coli* yielding a protein containing 192 amino acids. The N-terminal amino acid, methionine, is later removed to yield a protein that is chemically, immunologically and physicochemically identical to pituitary derived human growth hormone, consisting of 191 amino acids in a single polypeptide chain.

Growth hormone receptors are widely distributed throughout the body. The receptor activation is initiated by the binding of a single molecule of hGH to two hGH receptors, to form a ligand-binding-site-occupied by the hormone. The bioassay using the rat weight gain assay is an integral part of the control and definition of potency of each batch of rhGH. In children, hGH leads to increased growth velocity, pubescence and fertility.

The sponsor performed a 10-day potency (weight gain) test of _____ (Accretropin) in hypophysectomized rats. Sixteen hypophysectomized male Sprague-Dawley CD (CrI:CD(SD)Br) rats were administered subcutaneously either _____ or Humatrope at doses of 0, 0.1, 0.5 and 1.0 mg/kg/day for 10 days. Both _____ and Humatrope increased absolute body weight so that the two growth hormone products have similar pharmacological effects.

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2.6.2.2 Primary pharmacodynamics

Human growth hormone is a non-glycosylated, single chain, 191 amino acid, 22-Kilo-Dalton (kD) protein with two intramolecular disulphide bonds. Approximately 75% of pit-hGH is in this form and about 5-10% in a 20-KD form, formed by alternate splicing of messenger ribonucleic acid (RNA). All the effects of human growth hormone (hGH) are the result of its binding to a specific cell receptor which is widely distributed throughout the body. The mature receptor is a transmembrane glycoprotein containing a large N-terminal extracellular domain, which is responsible for binding of hGH, and a C-terminal cytoplasmic domain.

Growth hormone receptors are widely distributed throughout the body. The receptor activation is initiated by the binding of a single molecule of hGH to two hGH receptors, to form a ligand-binding-site-occupied by the hormone. The bioassay using the rat weight gain assay is an integral part of the control and definition of potency of each batch of rhGH.

Mechanism of action:

Growth hormone receptor activation is initiated by the binding of hGH to two hGH receptors, to form a ligand-binding-site-occupied receptor dimer. Receptor dimerisation leads to signal transduction, which is predominantly mediated by the non-receptor

tyrosine kinase, Jak2. It appears that the actions of hGH are either direct or mediated through insulin-like growth factors (IGF) -1 and -2 (IGF-1 and IGF-2), of which IGF-1 appears to be the more important because serum levels of IGF-1 are known to be reduced in hGH deficiency. IGF-2 may not play a dominant role in the action of growth hormone. Growth hormone stimulates proliferation and differentiation of progenitor cells.

Drug activity related to proposed indication:

The sponsor performed a 10-day potency (weight gain) test of _____ (Accretropin) in hypophysectomized rats under project# 88636. 16 Hypophysectomized male Sprague-Dawley CD (CrI:CD(SD)Br) rats were administered subcutaneously either _____ or Humatrope at doses of 0, 0.1, 0.5 and 1.0 mg/kg/day for 10 days. b(4)

Body weight gain was markedly increased in treated animals between Day 2 and 10, especially those receiving the test article at 0.5 or 1.0 mg/kg/day. At the dosage of 0.5 mg/kg/day, body weight gain was marginally greater in animals receiving Humatrope. Nevertheless, statistical analysis of data using the parallel line method indicates that the biological potency of _____ was not significantly different to that of Humatrope at the dosages examined in this hypophysectomized rat assay. Biological activity of Accretropin is performed by Cangene Corp. on the NB2 rat lymphoma cell line. This cell line arose from lymph nodes of an estrogenized male rat.

2.6.2.3 Secondary pharmacodynamics

No studies were conducted.

2.6.2.4 Safety pharmacology

The sponsor did not conduct safety pharmacology studies. However, previous safety pharmacology assessment of neurological, renal, pulmonary, and gastrointestinal effects of somatropin did not identify any significant liabilities.

2.6.2.5 Pharmacodynamic drug interactions

No pharmacodynamic drug interaction studies have been conducted with Accretropin.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

None

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary

Metabolic studies with ~~_____~~ (Accretropin) were not performed. Tissue distribution studies using radio-labeled Norditropin@ have shown that the majority of radioactivity is found in blood after 12 hours predominantly bound to erythrocytes. The TCA precipitable radioactivity made up 85% -95% of the total radioactivity in whole blood. The TCA precipitable radioiodinated material found in the liver made up 0.75 -1.6% of the dose. The kidneys contained 25 -50% of what was found in the liver. These results suggest that the growth hormone is mainly cleared through liver.

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There are few studies published on the absorption of exogenous growth hormone. A large variation is evident among individuals in different studies. The absorption appears to be more rapid from the intramuscular route (Tmax 2 -3 hours), with a disappearance phase from serum of 12 -20 hours as opposed to subcutaneous injections, which yield values of 4 -6 hours (T max) and 20-24 hours (disappearance) respectively. This difference has been confirmed in many studies.

Accretropin™ has been studied following subcutaneous administration in adult volunteers. Bioavailability of Accretropin™ was not determined. However, based on the bioavailability of other r-hGH products, bioavailability has been estimated at approximately 70% when administered subcutaneously. The volume of distribution of somatropin was not determined for Accretropin™. Somatropin is metabolized in the liver and kidneys. In the kidneys, hGH is broken down to its constitutive amino acids, which are then returned to the systemic circulation. Clearance was not determined for Accretropin™. The mean half-life of subcutaneously administered Accretropin™ is 3.63 hours. Urinary excretion of intact somatropin has not been measured.

Summary of somatropin pharmacokinetic parameters in the normal population following a 4 mg dose of Accretropin™ administered subcutaneously* below.

	AUC _(0-t) (ng·h/mL)	AUC _(0-inf) (ng·h/mL)	C _{max} (ng/mL)	T _{max} (h)	t _{1/2} (h)
mean ± SD	238.09 ± 44.11	255.31 ± 43.03	29.49 ± 8.32	3.50 ± 1.20	3.63 ± 1.33

*Abbreviations: AUC_{0-t}=area under the curve until 24 hours after administration; AUC_{0-inf}=area under the curve to infinity; C_{max}=maximum concentration; t_{1/2}=half-life; T_{max}=time to maximum concentration (given as the median value); SD=standard deviation

2.6.4.2 Methods of Analysis

Not applicable, as all studies were either published or conducted by a contract research organizations.

2.6.4.3 Absorption

Absorption —Accretropin™ has been studied following subcutaneous administration in adult volunteers. Bioavailability of Accretropin™ was not determined. However, based on the bioavailability of other r-hGH products, bioavailability has been estimated at approximately 70% when administered subcutaneously

2.6.4.4 Distribution

The volume of distribution of somatropin was not determined for Accretropin™.

2.6.4.5 Metabolism

Extensive metabolism studies have not been conducted. Somatropin is metabolized in the liver and kidneys. In the kidneys, hGH is broken down to its constitutive amino acids, which are then returned to the systemic circulation. Clearance was not determined for Accretropin™. The mean half-life of subcutaneously administered Accretropin™ is 3.63 hours as shown below.

Table 1: Summary of somatropin pharmacokinetic parameters in the normal population following a 4 mg dose of Accretropin™ administered subcutaneously*

	AUC _(0-t) (ng·h/mL)	AUC _(0-inf) (ng·h/mL)	C _{max} (ng/mL)	T _{max} (h)	t _{1/2} (h)
mean ± SD	238.09 ± 44.11	255.31 ± 43.03	29.49 ± 8.32	3.50 ± 1.20	3.63 ± 1.33

*Abbreviations: AUC_{0-t}=area under the curve until 24 hours after administration; AUC_{0-inf}=area under the curve to infinity; C_{max}=maximum concentration; t_{1/2}=half-life; T_{max}=time to maximum concentration (given as the median value); SD=standard deviation

2.6.4.6 Excretion

Urinary excretion of intact somatropin has not been measured.

2.6.4.7 Pharmacokinetic drug interactions

No study was conducted by the sponsor.

2.6.4.8 Other Pharmacokinetic Studies

The sponsor included a table that has some relevant pharmacokinetic data, which were obtained from the published report on norditropin and other growth hormone in rats and monkeys as shown below.

Table 2.6.4.1a Pharmacokinetic Studies from published report for Norditropin® and other growth hormone preparations in Rats and Cynomolgus monkeys

Species/ Drug	Route of Administration	Dose (ug/kg)	Observations		
			Parameter	Animals	
Rat Norditropin® (Jorgensen et al., 1988)				Hypophysectomized rats	Sham Controls
	Subcutaneous	100	-AUC (ng/min/mL)	7580 (7100 - 8060) 2820	(2340 - 3300)
	Intravenous	60	-AUC (ng/min/mL) -Clearance (mL/kg/min) -T _{1/2α} (min) -T _{1/2β} (min)	18120 3.5 3 - 7 29	8180 7.5
Cynomolgus Monkeys Recombinant GH (Moore et al., 1988)	Subcutaneous	124	-AUC (ng/min/mL) -Peak Concentration (ng/mL) -Time to peak of mean (min)	31000 ± 7300 71 ± 23 420	
Met -hGH (Protropin) (Moore et al., 1988)	Subcutaneous	133	-AUC (ng/min/mL) -Peak Concentration (ng/mL) -Time to peak of mean (min)	30000 ± 4400 66 ± 15 420	
Cynomolgus Monkeys Recombinant GH (Moore et al., 1988)	Intravenous	124	-AUC (ng/min/mL) -Clearance (mL/kg/min) -T _{1/2α} (min) -T _{1/2β} (min)	34000 ± 7000 15 ± 3 8.6 ± 1.4 77 ± 32	
Met -hGH (Protropin) (Moore et al., 1988)	Intravenous	133	-AUC (ng/min/mL) -Clearance (mL/kg/min) -T _{1/2α} (min) -T _{1/2β} (min)	40000 ± 8000 13 ± 3 8.7 ± 1.1 66 ± 27	

2.6.4.9 Discussion and Conclusions

The sponsor did not perform separate metabolic studies in animals because the PK parameters of rhGH are well documented in animals as well as in human.

2.6.4.10 Tables and figures to include comparative TK summary

None.

2.6.5 PHARMACOKINETICS TABULATED SUMMARY

None.

SPECIAL POPULATIONS

Geriatric — The pharmacokinetics of Accretropin™ has not been studied in patients greater than 65 years of age. Limited published data suggests that the plasma clearance and average steady-state plasma concentration of r-hGH may not be different between young and elderly patients.

Pediatric — The pharmacokinetics of r-hGH in pediatric patients is similar to adults.

Gender — No studies have been performed with Accretropin™. The available literature indicates that the pharmacokinetics of growth hormone is similar in both men and women.

Race — No data are available.

Renal, Hepatic insufficiency — No studies have been performed with Accretropin™.

2.6.6 TOXICOLOGY

2.6.6.1 Overall toxicology summary

Evaluation of the toxicity profile of Accretropin has included single- and repeated-dose toxicity. Genotoxicity, reproductive toxicity and carcinogenicity studies as well as local tolerance and antigenicity were not performed. Single dose studies showed that Accretropin (somatropin) was essentially without effects in Albino rats except observations of body weight gains as expected.

General toxicology:

An acute single dose and subacute 10 day toxicity study was conducted in albino rats. A maximum dose of 2.5 mg/kg was found to produce no treatment or dose related clinical signs after one day of treatment and 14-day observation period in the acute group or after 10 days of treatment in the subacute group of rats as shown below.

A 30-day subchronic toxicity study was also conducted in albino rats. A maximum dose of 2.5 mg/kg/day of Accretropin™ did not produce clinical signs of toxicity except for histopathological lesions in the injection site. Treated animals in both groups achieved higher mean body weights and body weight gain than the respective control animals; usually attaining statistical significance. A slight increase in food consumption was noted in males and females receiving Accretropin™ during the treatment period, usually attaining statistical difference.

Table 2.6.6.1a Toxicology Program for Accretropin™

Study Type and Duration	Route of Administration	Species	Drug Administered, Contract Research Organization and Study Number
Acute Single and Subacute 10-Day	SC	Albino Rat	Accretropin™, _____ Project No. 88637 ¹
Subchronic 30-Day	SC	Albino Rat	Accretropin™, _____ Project No. 88929 ²

¹ Vol 2, Module 4.2.3.2.1 An Acute Single and Subacute 10-Day Repeated Dose Subcutaneous Injection Toxicity Study of _____ in the Albino Rat – _____ Project No. 88637, pg. 1. In subsequent text this study will be referred to as Study 88637.

² Vol 3, Module 4.2.3.2.2 A 30-Day Subcutaneous Injection Toxicity Study with _____ in the Albino Rat – _____ Project No. 88929, pg. 1. In subsequent text this study will be referred to as Study 88929.

b(4)

b(4)

2.6.6.2 Single-dose toxicity

An acute single dose and subacute 10-day repeated dose subcutaneous injection toxicity study (study#88637) of _____ (Accretropin) were conducted in Sprague-Dawley CD (CrI:CD(SD)BR) rats under GLP condition at Cangene Corp., Winnipeg, Manitoba, Canada on April 20, 1999. Five male and five female rats were administered _____ subcutaneously at dose of 0, 0.5 and 2.5 mg/kg/day once or for 10 days as shown below.

b(4)

Group Identification	Dose level (mg/kg/day)	Dose Volume (mL/kg/day)	Number of doses	Number of Animals	
				Male	Female
1 Control	0	2	1	5	5
2	0.5	2	1	5	5
3	2.5	2	1	5	5
4 Control	0	2	10	5	5
5	0.5	2	10	5	5
6	2.5	2	10	5	5

b(4)

The following were evaluated: clinical observations, body weight, food consumption, hematology, clinical biochemistry, antibody levels (to be reported separately by Sponsor), organ weights, macroscopic observations at necropsy and histopathology (multiple dose animals only).

Key study findings:

There were no treatment-related clinical signs, morbidity or mortality during the study. There were no effects on body weight or body weight gain following a single dose of _____. But, there was a slight increase in body weight gain in 10-day repeated dose group. There were no treatment-related effects on food consumption in animals given either a single dose or multiple doses of _____. There were no treatment-related effects on hematology and clinical chemistry parameters in animals given either a single dose or multiple doses.

b(4)

There were no toxicologically significant differences in organ weights following either a single dose or multiple doses of _____. There were no treatment-related gross pathological findings following either single or repeated administration and there were no treatment-related histopathological findings following 10-day repeat administration.

It appears that a dose level of 2.5 mg/kg/day was considered to be the no toxic effect level following daily administration for up to 10 days in rats.

2.6.6.3 Repeat-dose toxicity

4-Week Repeated Subcutaneous Dose Toxicity Study with hGH in Albino Rats b(4)

Key study findings:

Ten Sprague-Dawley CD (CrI:CD(SD)BR) rats/sex/group were administered subcutaneously at doses of 0, 0.5 and 2.5 mg/kg/day for 4 weeks. Control animal had vehicle at a dose volume of 2 ml/kg. There were no deaths in all groups. There were no treatment-related effects on clinical observations, hematology, and blood chemistry. Body weight gains or organ weights were increased, depending upon doses in the HD groups of animals. There were no gross lesions and histopathological findings as a result of the treatment except injection sites. b(4)

Study no.: 88929

Conducting laboratory and location: Cangene Corp., Winnipeg, Manitoba, Canada

Date of study initiation: 11/11/1999

GLP compliance: Yes

QA report: yes (x) no ()

Drug, lot #, and % purity: Lot#4412803

Methods

Doses: 0(vehicle), 0.5 and 2.5 mg/kg/day (Please see the table below)

Species/strain: Rat/ Sprague-Dawley CD (CrI:CD(SD)BR)

Number/sex/group or time point (main study): 10 rats/sex/group

Route, formulation, volume, and infusion rate: Subcutaneous, the injection volume was 2 ml/kg/day.

Satellite groups used for toxicokinetics or recovery: None

Age: 4 Weeks

Weight: Males 179-224 g; Females 138-163 g on arrival

Group No. Identification	Dose Level (mg/kg/day)	Dose Volume (mL/kg/day)	No. of animals (sex/group)	Animal ID	
				Males	Females
1 Vehicle Control	0	2	10	1001-1010	1501-1510
2	0.5	2	10	2001-2010	2501-2510
3	2.5	2	10	3001-3010	3501-3510

b(4)

Observations and times:

Mortality: Twice a day

Clinical signs: Daily

Body weights: Days -1, 3, 7, 10, 14, 17, 21, 24, 28 and 30

Food consumption: Weekly

Ophthalmoscopy: Ophthalmoscopy was done two times in all animals before treatment and after final administration. A complete fundoscopic (indirect ophthalmoscopy) and bioinicroscopic (slit lamp) examination were performed on all animals during the pretreatment period and "during Week 4.

EKG: NA

Hematology: Before autopsy, animals fasted overnight were ether anaesthetized. The sponsor took a blood sample from the abdominal aorta.

Clinical chemistry: From the posterior venous blood sample taken, the sponsor separated serum by centrifugation (3000 rpm, for 10 min) for the biochemical lab tests.

Urinalysis: In all animals which were going to be sacrificed, urinalysis was performed after the final administration. Specific gravity, pH, protein, glucose, ketone body, occult blood, bilirubin, urobilinogen, etc.

Gross pathology: For all animals on which autopsy was performed, the sponsor took the following internal organs and fixed them with 10 % neutral formalin solution (skin as well as testis and sternum were treated with Bouin's solution). In general, the samples were stained with hematoxylin-eosin before the gross pathological examination.

Organ weights (specify organs weighed if not in histopath table): Conventional methods were used.

Histopathology: Adequate Battery: yes (x), no ()—explain

Peer review: yes (x), no ()

Results

Mortality: No death in all groups.

Clinical Signs: There were no treatment related clinical signs except crust formation and local hair loss at the injection sites as shown below.

Body Weight:

Mean body weights in female group 3 (High Dose group) were significantly increased in Weeks 1, 2, and 3 as shown below. There were no such changes in any male groups.

TABLE NO.: 1
PROJECT NO.: 88929

BODY WEIGHTS (G) - SUMMARY OF MEANS

GROUP 1 VEHICLE CONTROL			GROUP 3 2.5 MG/KG/DAY			
GROUP 2 0.5 MG/KG/DAY						
MALES			SEX GROUP	FEMALES		
1	2	3		1	2	3
141.7	143.9	143.0	DAY -8	117.7	117.5	116.9
196.3	202.5	197.0	DAY -1	148.0	148.7	149.8
218.2	227.3	221.4	DAY 3	159.7	159.3	164.9
246.3	258.8	253.9	DAY 7	172.1	174.5	187.8 B
266.6	280.2	276.8	DAY 10	180.0	186.0	204.5 B
293.0	309.7	309.1	DAY 14	193.2	200.0	223.6 B
312.0	328.7	331.4	DAY 17	202.0	203.6	235.1 B
332.0	347.8	354.6	DAY 21	210.4	213.0	250.8 B
347.3	366.1	373.7	DAY 24	217.9	219.5	259.2 B
351.9	368.3	381.4	DAY 28*	218.1	219.4	257.4 B
367.3	387.3	397.2	DAY 30	226.1	227.0	268.3 B

b(4)

SIGNIFICANTLY DIFFERENT FROM CONTROL (GROUP 1) VALUE: B - P<.01 (DUNNETT'S)
* Selected animals were food and water deprived for urinalysis determination

Food consumption: There were significant increases in the parameter in male groups 3 and 2 on Week 3. In females, there was a significant increase in food consumption in group 3 from Week 1 as shown below.

TABLE NO.: 3
PROJECT NO.: 88929

FOOD CONSUMPTION (GRAMS/ANIMAL) - SUMMARY OF MEANS

GROUP 1 VEHICLE CONTROL			GROUP 3 2.5 MG/KG/DAY			
GROUP 2 0.5 MG/KG/DAY						
MALES			SEX GROUP	FEMALES		
1	2	3		1	2	3
183.1	198.2	183.7	D -8- 1	153.7	158.3	150.6
168.2	182.7	174.1	1- 8	130.8	131.1	141.3 A
184.3	200.4	196.5	A 8- 15	141.7	144.7	156.4 A
191.3	211.1A	211.0 A	15- 22	142.9	146.9	161.2 B
173.4	195.3B	196.6 B	Y 22- 29	132.1	134.6	145.8 A

b(4)

SIGNIFICANTLY DIFFERENT FROM CONTROL (GROUP 1) VALUE: A - P<.05 · B - P<.01 (DUNNETT'S)

Ophthalmic exam: There were no abnormal findings during the study. There were no treatment-related ocular changes during the treatment phase. Minor findings were observed in a few animals. They were considered incidental in origin and unrelated to treatment since they have been routinely found in comparable rat populations.

Hematology: In males, erythrocyte indices such as MCH and MCHC were increased significantly in group 2 and 3 rats in Week 4. The increases in MCHC were also noted in

TABLE NO. 4 GROUP MEAN (S.D.) HEMOGRAMS PROJECT NO:

DAY 31 - MALES

	PLT ₃ X10 ³	MPV ₃ UM	RETIC %	PT SEC.	APTT SEC.
GROUP 1 - VEHICLE CONTROL	991.7 95.06	8.5 .35	.7 .61	16.0 1.00	26.1 2.09
GROUP 2 - 0.5 MG/KG/DAY	918.9 108.84	8.6 .62	.6 .33	15.7 .49	22.7 B 1.54
GROUP 3 - 2.5 MG/KG/DAY	972.9 68.74	8.3 .52	.6 .42	15.6 .58	23.6 B 1.11

b(4)

SIGNIFICANTLY DIFFERENT FROM CONTROL (GROUP 1) VALUE: B - P<.01 (DUNNETT'S)

TABLE NO. 4 GROUP MEAN (S.D.) HEMOGRAMS PROJECT NO

DAY 31 - FEMALES

	WBC ₃ X10 ³	NEUT SEG %	WBC DIFFERENTIAL COUNT				BASO %
			NEUT NSEG %	LYMPH %	MONO %	EOSIN %	
GROUP 1 - VEHICLE CONTROL	4.9 1.43	8.2 3.46	0.0 0.00	89.3 3.62	1.2 .92	1.2 1.40	.1 .32
GROUP 2 - 0.5 MG/KG/DAY	5.6 1.78	8.5 3.31	0.0 0.00	88.6 2.95	1.9 1.10	1.0 .82	0.0 0.00
GROUP 3 - 2.5 MG/KG/DAY	7.2 B 1.26	9.5 8.24	0.0 0.00	87.5 9.63	1.9 1.37	1.1 .88	0.0 0.00

b(4)

SIGNIFICANTLY DIFFERENT FROM CONTROL (GROUP 1) VALUE: B - P<.01 (DUNNETT'S)

TABLE NO. 4 GROUP MEAN (S.D.) HEMOGRAMS PROJECT NO

DAY 31 - FEMALES

	RBC ₆ X10 ⁶	Hb G/DL	Ht %	MCV ₃ UM	MCH PG	MCHC G/DL	RDW %
GROUP 1 - VEHICLE CONTROL	7.06 .514	14.2 .97	41.2 2.75	58.4 1.31	20.1 .61	34.5 .60	11.3 .37
GROUP 2 - 0.5 MG/KG/DAY	6.99 .341	14.4 .58	40.7 1.67	58.3 1.31	20.7 .70	35.4 A .83	11.7 .62
GROUP 3 2.5 MG/KG/DAY	6.97 .244	14.6 .45	41.0 1.17	58.9 1.29	21.0 A .71	35.5 B .69	11.9 A .53

SIGNIFICANTLY DIFFERENT FROM CONTROL (GROUP 1) VALUE: A - P<.05 B - P<.01 (DUNNETT'S)

b(4)

TABLE NO. 4

GROUP MEAN (S.D.) HEMOGRAMS

DAY 31 - FEMALES

	PLT ₃ X10 ³	MPV ₃ UM	RETIC %	PT SEC.	APTT SEC.
GROUP 1 - VEHICLE CONTROL	842.1 130.34	8.3 .41	.4 .50	15.4 .49	23.1 3.54
GROUP 2 - 0.5 MG/KG/DAY	1001.9 A 124.93	8.0 .36	.5 .23	15.1 .68	21.6 1.54
GROUP 3 - 2.5 MG/KG/DAY	980.5 A 122.09	8.5 .28	.3 .22	15.3 1.59	21.8 1.76

b(4)

SIGNIFICANTLY DIFFERENT FROM CONTROL (GROUP 1) VALUE: A - P<.05 (DUNNETT'S)

Blood chemistry: In males, total cholesterol was increased significantly in all treated groups as shown below, although there were no such changes in female rats. In females, albumin and A/G ratio were reduced in the HD group only.

TABLE NO. 5 GROUP MEAN (S.D.) CLINICAL BIOCHEMICAL ANALYSES PROJECT NO. 1
 DAY 31 - MALES

	ALT U/L	ALP U/L	CA MG/DL	PHOS MG/DL	CHOL MG/DL
GROUP 1 - VEHICLE CONTROL	26.0 3.43	166.2 38.24	9.7 .24	8.34 .539	49.1 6.38
GROUP 2 - 0.5 MG/KG/DAY	26.6 2.99	145.8 29.02	9.7 .18	8.38 .541	70.4 B 13.03
GROUP 3 - 2.5 MG/KG/DAY	27.4 5.62	154.8 27.35	9.9 .29	8.55 .524	73.0 B 12.17

SIGNIFICANTLY DIFFERENT FROM CONTROL (GROUP 1) VALUE: B - P<.01 (DUNNETT'S)

b(4)

TABLE NO. 5 GROUP MEAN (S.D.) CLINICAL BIOCHEMICAL ANALYSES PROJECT NO. 8
 DAY 31 - MALES

	TRIG MG/DL	T PROT G/DL	ALB G/DL	A/G RATIO	GLOB G/DL
GROUP 1 - VEHICLE CONTROL	43.0 23.99	5.8 .26	3.0 .10	1.05 .053	2.8 .19
GROUP 2 - 0.5 MG/KG/DAY	40.1 10.08	5.9 .12	2.9 .04	.96 B .050	3.0 .13
GROUP 3 - 2.5 MG/KG/DAY	49.9 18.78	5.9 .24	3.0 .08	1.05 .059	2.9 .19

SIGNIFICANTLY DIFFERENT FROM CONTROL (GROUP 1) VALUE: B - P<.01 (DUNNETT'S)

b(4)

TABLE NO. 5 GROUP MEAN (S.D.) CLINICAL BIOCHEMICAL ANALYSES PROJECT NO : 8
 DAY 31 - FEMALES

	TRIG MG/DL	T PROT G/DL	ALB G/DL	A/G RATIO	GLOB G/DL
GROUP 1 - VEHICLE CONTROL	35.9 10.68	5.9 .36	3.2 .19	1.14 .069	2.8 .21
GROUP 2 - 0.5 MG/KG/DAY	33.6 9.25	6.1 .30	3.1 .16	1.07 .066	2.9 .19
GROUP 3 - 2.5 MG/KG/DAY	36.1 10.49	6.0 .33	3.0 A .13	1.00 B .060	3.0 .23

b(4)

SIGNIFICANTLY DIFFERENT FROM CONTROL (GROUP 1) VALUE: A - P<.05 B - P<.01 (DUNNETT'S)

Urinalysis: No significant changes were noted.

Organ weights: In male rats, absolute weights of adrenal, spleen and thymus were increased in all treated groups, which were not observed in the female rats. In addition, the weights of lung in the HD group male rats were also increased. In females, the weights of liver, heart, lung, kidney and gonad were increased in the HD groups only as shown below.

Effects of Accretropin) on Organ Weights in 4-Week Toxicity Study in Rat@						
Sex	Male			Female		
Dose (mg/kg/day)	0	0.5	2.5	0	0.5	2.5
Body Weight (g)	335	357	365	207	208	247*
Liver	9.2	10.0	10.5	5.9	6.3	7.3*
Spleen	0.7	0.8*	0.8*	0.5	0.5	0.6
Heart	1.3	1.4	1.4	0.9	0.9	1.0*
Lung	1.4	1.5	1.5*	1.0	1.0	1.2*
Thyroids/Parathyroids	0.020	0.022	0.022	0.015	0.015	0.017
Adrenals	0.051	0.053*	0.071*	0.063	0.061	0.065
Kidneys	2.4	2.5	2.6	1.6	1.6	1.8*
Gonads	3.2	3.2	3.2	0.087	0.083	0.103*
Prostate	0.86	0.78	0.88			
Uterus				0.43	0.48	0.39
Brain	2.0	2.0	2.0	1.9	1.9	1.9
Pituitary	0.01	0.01	0.01	0.01	0.01	0.01
Thymus	0.49	0.59*	0.60*	0.36	0.40	0.45

*N=10 in all groups. *Indicates p<0.05, compared to the control.

b(4)

Gross necropsy findings

According to the pathologist's report, gross pathological finding most frequently observed was single to multiple dark areas noted at the injection sites in 7/10 males and 6/10 females at 2.5 mg/kg/day; 3/10 males at 0.5 mg/kg/day and 3/10 females and 1/10 male in the vehicle control group as shown below.

Other gross findings observed dark area(s) in the colon, lung, thymus, and/or stomach; pale area (s) in the liver, heart, and/or kidney; enlarged spleen and/or mandibular lymph node, a cyst within the mandibular lymph node; depressed area in the kidney, dilated renal pelvis or thickening of the urinary bladder. All these were considered spontaneous in origin and not considered to be related to treatment, according to the sponsor.

INCIDENCE OF NECROPSY FINDINGS BY ORGAN/GROUP/SEX

		MALE		
ORGAN/FINDING	DOSE GROUP:	1	2	3
	ANIMAL EXAMINED:	10	10	10
COLON	:			
- -Area dark-	:	-	-	1
INJECTION SITE	:			
- -Area dark-	:	1	3	7
KIDNEY	:			
- -Area depressed-	:	-	1	-
- -Area pale-	:	-	1	-
- -Dilatation pelvis-	:	2	-	1
LIVER	:			
- -Area pale-	:	1	-	-
LUNG	:			
- -Area dark-	:	1	-	-
L.NODE MANDIBULAR	:			
- -Cyst-	:	-	1	-
- -Enlargement-	:	1	-	-
SPLEEN	:			
- -Enlargement-	:	-	1	-
STOMACH	:			
- -Area dark-	:	1	-	-
THYMUS	:			
- -Area dark-	:	1	-	-

TABLE NO.: 8

PROJECT NO.:

INCIDENCE OF NECROPSY FINDINGS BY ORGAN/GROUP/SEX

		FEMALE		
ORGAN/FINDING	DOSE GROUP:	1	2	3
	ANIMAL EXAMINED:	10	10	10
HEART	:			
- -Area pale-	:	1	-	-
INJECTION SITE	:			
- -Area dark-	:	3	-	6
KIDNEY	:			
- -Area depressed-	:	-	1	-
- -Dilatation pelvis-	:	-	-	1
LIVER	:			
- -Area pale-	:	1	3	2
THYMUS	:			
- -Area dark-	:	1	2	1
URINARY BLADDER	:			
- -Thickening-	:	-	1	1

2.1. Microscopic Findings:

Histopathological findings: Histopathological findings were limited to the injection sites, although there were some sporadic changes in a few organs, which appear not related to the treatment. A major histopathological treatment-related change was areas of hemorrhage at the injection sites in 6/10 males and 6/10 females at 2.5 mg/kg/day. These changes were observed in all groups with a greater incidence and severity at 2.5 mg/kg/day. Mononuclear cell infiltrate was noted at the injection sites with an apparent dose-related response in incidence and severity; 8/10 males and 6/10 females at 2.5 mg/kg/day; 6/10 males and 6/10 females at 0.5 mg/kg/day and 2/10 males and 3/10 females in the vehicle control group.

The dark areas at injection sites were areas of hemorrhage and were present in all groups, though more common and more severe in the 2.5 mg/kg/day group (6/10 male animals, 6/10 female animals). Areas of mononuclear cell infiltration were also present at injection sites in all groups, with an apparent dose-related increase in incidence severity (8/10 male animals and 6/10 female animals in the 2.5 mg/kg/day group, 6/10 male animals and 6/10 female animals in the 0.5 mg/kg/day group, and 2/10 male animals and 3/10 female animals in the vehicle control group. A single male animal in the 2.5 mg/kg/day group also had an area of neutrophilic infiltration at one injection site.

A single male animal in the 2.5 mg/kg/day group had a mononuclear infiltrate of moderate severity at one of the injection sites and a single female animal in the same dosage group had a hemorrhage of moderate severity at two of the injection sites. In a small number of cases, more than one injection site within a single animal was affected in both the 0.5 mg/kg/day and 2.5 mg/kg/day groups, whereas only single injection sites per animal were affected in the vehicle control group. The other histopathological changes noted were considered to be background lesions and were present in only very small numbers of animals in various groups. It appears that all the changes are minor and not related to the treatment.

Histopathology: Adequate Battery: yes (x), no ()

2.6.6.4 Genotoxicity
No genetic toxicity study was performed

2.6.6.5 Carcinogenicity
No carcinogenicity study was performed.

2.6.6.6 Reproductive and developmental toxicology
No relevant reproductive study was performed.

2.6.6.7 Local tolerance

No local tolerance studies have been performed. However, the sponsor added the following statement. Pain perception and local tissue reactions following injections are dependant on the preservative used in the formulations of Growth Hormones. Accretropin contains 3.4mg/mL of phenol in the formulation. Solutions of other growth hormone preparations for subcutaneous injections contain phenol as the preservative (Nutropin AQ). In toxicological studies, no or only mild reactions have been observed following subcutaneous administration of phenol at 7.5mg/mL. This concentration is well above the concentration of phenol in Accretropin (3.4mg/mL).

2.6.6.8 Special toxicology studies:

No antigenicity studies were conducted by the sponsor in animals. The sponsor conducted two human immunogenicity studies with ——. 22 out of the 44 subjects and 19 out of 37 subjects, respectively, developed anti-hGH antibodies during 36 months of treatment with ——. In 9 subjects in study GA-005/5A and 8 subjects in study GA-00m A, there was an undetectable level of anti-ECP antibodies at baseline, with a positive result developing during the studies. **b(4)**

The height velocity for the subjects with a positive anti-hGH and/or anti-ECP

result was higher at the evaluated endpoints than the baseline (pre-treatment) height velocity. The data indicate that the height velocity was not affected developing anti-hGH and/or anti-ECP antibodies against _____ which suggests that these antibodies were not neutralizing in nature. A detailed listing with the comparison to local and international growth standards for healthy age and gender matched children for both studies. b(4)

2.6.6.9 Discussion and Conclusions

Pharmacology of _____ (Accretropin) for its potency was compared with Humatrope in hypophysectomized rats. It appears that _____ is comparable to Humatrope in terms of body weight gains. General toxicity study for four weeks in rats indicates that _____ has no remarkable effects on clinical signs. It increased body weight gain at the dose of 2.5 mg/kg/day (the top dose group). There were minor effects of _____ on hematology and serum chemistry parameters, which appear not related to the treatment. There were no genetic, carcinogenic and reproductive toxicity studies with Accretropin, although the effects of growth hormones are well documented in published literature. The reviewers can safely conclude that the preclinical data support the NDA. b(4)

2.6.6.10 Tables and Figure

2.6.7 TOXICOLOGY TABULATED SUMMARY

None.

OVERALL CONCLUSIONS AND RECOMMENDATIONS

Conclusions: There are no preclinical pharmacology and toxicology issues with this Accretropin NDA.

Unresolved toxicology issues (if any): None.

Recommendations: Pharmacology and toxicology data support approval of this NDA.

Suggested labeling: Please see "Pharmacology Recommendation" above.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature _____ Concurrence Yes ___ No ___

APPENDIX/ATTACHMENTS:

The sponsor provided the following contraindication and warning information on Accretropin, which may apply to other growth hormones.

CONTRAINDICATIONS

b(4)

1 Page(s) Withheld

 Trade Secret / Confidential (b4)

X Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

Withheld Track Number: Pharm/Tox-

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Herman Rhee
2/8/2007 08:35:03 AM
PHARMACOLOGIST

Karen Davis-Bruno
2/8/2007 08:43:27 AM
PHARMACOLOGIST

**45 Day Meeting Checklist
NONCLINICAL PHARMACOLOGY/TOXICOLOGY**

NDA No. 21-538/Cangene/Accretropin(rh Growth Hormone)/July 9, 2006

ITEM	YES	NO	COMMENT
1) Does this section of the NDA appear to be organized (according to 21 CFR 314 and current guidelines for format and content) in a manner that would allow a substantive review to be completed?	X		
2) Is this section of the NDA indexed and paginated in a manner to enable a timely and substantive review?	X		
3) Is this section of the NDA sufficiently legible so that a substantive review can be done? Has the data been presented in an appropriate manner (consider tables, graphs, complete study reports, inclusion of individual animal data, appropriate data analysis, etc.)?	X		
4) Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission communications/discussions, completed and submitted in this NDA? Please itemize the critical studies included and indicate any significant studies that were omitted from the NDA (None)	X		<p>Have electronic files of the carcinogenicity studies been submitted for statistical review? N/A</p> <p>Studies completed:</p> <p>1) A 10-Day weight gain study of _____ sc injection in hypophysectomized rats</p> <p>2) A 30-Day SC toxicity study of _____ in Albino rats</p> <p>3) No long-term toxicology studies</p> <p>4) No carcinogenicity study</p> <p>5) No genotoxicity study</p> <p>6) Reproductive & developmental toxicity studies</p> <p>7) No antigenicity study</p>

b(4)

			8) No immunotoxicity studies 9) No mechanistic study 10) No dependence, metabolites and special studies
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ITEM	YES	NO	COMMENT
5) Were the studies adequately designed (ie., appropriate number of animals, adequate monitoring consistent with the proposed clinical use, state-of-the art protocols, etc.)?	X		
6) If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the impurity profiles), has the sponsor clearly defined the differences and submitted reviewable supportive data (ie., adequate repeat studies using the marketed product and/or adequate justification for why such repetition would not be necessary)?	X		

<p>7) Does the route of administration used in animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route?</p>	<p>X</p>		
<p>8) Has the proposed draft labeling been submitted? Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.577? Is information available to express human dose multiples in either mg/m² or comparative serum/plasma AUC levels?</p>	<p>X</p>		

ITEM	YES	NO	COMMENT
9) From a pharmacology/toxicology perspective, is this NDA fileable? If not, please state in item # 10 below why it is not.	X		
10) Reasons for refusal to file:			

Herman Rhee, Ph.D.

 Reviewing Pharmacologist

Jeri Elhage, Ph.D.

 Supervisory Pharmacologist

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Herman Rhee
6/12/2006 08:00:50 AM
PHARMACOLOGIST

Jeri El Hage
6/12/2006 09:02:58 AM
PHARMACOLOGIST