

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-106

Pharmacology Review(s)

PHARMACOLOGY/TOXICOLOGY COVER SHEET

NDA number: 21-105

Review number: 3

Sequence number/date/type of submission: N000BP, Sept 24, 02

Information to sponsor: Yes (x) No ()

Sponsor and/or agent: Pharmacia & Upjohn, 7000 Portage Road, Kalamazoo, MI 49001-0199

Manufacturer for drug substance : B2036-PEG was originally manufactured by Genentech (P1).
Later, sponsor switched manufacturer to _____
_____ Pharmacia Upjohn (Kalamazoo, MI) recently acquired Sensus
(2/29/2001) and it is now the manufacturer of the more pure P3 product.

Reviewer name: Fred Alavi, Ph.D.

Division name: Metabolic and Endocrine Drug Products

HFD #: 510

Review completion date: Nov 27, 02

Drug:

Trade name: Somavert ®

Generic name: pegvisomant, rhGH antagonist (PEGylated)

Code name: B2036-PEG

Chemical name:

CAS registry number:

Mole file number:

Molecular formula/molecular weight: B2036-PEG is a 191 amino acid polypeptide with two disulfide bonds similar to human GH. There are 4-5 PEG moieties (~5000 Dalton each) covalently bound to amino groups on the surface of the molecules. This increases its mass to 42-46,000Da.

Relevant INDs/NDAs/DMFs: IND _____ and IND _____ (for diabetes indication)

Drug class: GH antagonist, pegylated

Indication: Acromegaly (third line treatment)

Clinical formulation: Per vial:

10 mg B2036 protein (white lyophilized powder stable for 6 months at 2-8°C)

36 mg Mannitol, 1.36 mg glycine, 1.04 mg Sodium phosphate dibasic anhydrous

0.36 mg Sodium phosphate monobasic monohydrate, to be reconstituted in sterile water (1 ml) to 10 mg/ml, pH 7.4

Route of administration: SC daily

Proposed use: For treatment of acromegaly

Disclaimer: Use of sponsor's material was restricted to PK/TK and other data tables. Scanned tables pasted as images in the review can be easily recognized by their appearance in the review. Some of the introductory text that was found to represent the drug background accurately were modified and incorporated into the pharmacology section.

AP
W/P4

Executive Summary

I. Recommendations

- A. Recommendation on Approvability: A two-year carcinogenicity must be completed as a Phase IV commitment**
- B. Recommendation for Nonclinical Studies: A two-year carcinogenicity must be completed as a Phase IV commitment. The sponsor should submit a carcinogenicity protocol for review by the Executive Carcinogenicity Assessment Committee.**
- C. Recommendations on Labeling: as stated in the original NDA review. Carcinogenesis, Mutagenesis, impairment of fertility:**

Pregnancy: Pregnancy category B:

II. Summary of Nonclinical Findings:

Brief Overview of Nonclinical Findings:

- A. The sponsor had submitted a 4-WK bridging study in rats comparing the maximum dose of P2 (30 mg/kg/day) used in the 6-month toxicity study to new P3 product (10 and 30 mg/kg/day). The major findings were consistent with the 6 month rat study: inflammation at the injection site with minor decreases in lymphocytes and white blood cells with both 30 mg/kg/d P2 and P3 product. The injection site inflammations were dose dependent, more prominent in males and clearly drug related. There was no clear evidence to support or dismiss renal findings noted in the 6-month rat study. However, there was one incidence of minimal renal cortical tubular vacuolation in a 30 mg/kg/d P3 treated female. One high dose male had marked testicular atrophy. The increase in adrenal gland weight noted in the 6-month study was also observed with both doses of P3 and P2. These concerns will be clarified with the 2-year rat bioassay to be conducted as a phase IV requirement. The AUC values in both male and female rats increased by 6 to 8 fold from day 1 to day 28. The females had significantly greater drug exposure than males contrary to findings in the 6 month rat toxicity study. The 30 mg/kg/d P3 produced exposures in rats approximately 31 to 48 fold greater than daily drug exposure (AUC) in acromegalic subjects dosed with 20 mg/day. Overall there were no significant differences in toxicological profile of 30 mg/kg/d P3 and P2 product. The injection site inflammations were drug related and dose dependent as noted earlier with P2 product in the 6 month rat and monkey studies.**

- B. Pharmacologic Activity: Pegvisomant (B2036-PEG) is a human GH antagonist that actively binds to monkey and rabbit GH receptor but with very low affinity to rat or mice GH receptors. As a GH receptor antagonist, pegvisomant prevents GH related increase in insulin like growth factor-1 (IGF-1) thus preventing GH-induced acromegaly in humans.
- C. Nonclinical Safety Issues Relevant to Clinical Use: There appears to be little difference in the toxicological profiles of the new P3 and the previous P2 product. The single 2-year bioassay required as part of phase IV commitment, should clearly demonstrate any possible renal safety concern with pegvisomant, a pegylated growth hormone antagonist.

III. Administrative

A. Reviewer signature: Fred Alavi, Ph.D.

B. Supervisor signature: Concurrence - Jeri El Hage, Ph.D.

Non-Concurrence - _____
(see memo attached)

C. cc: list:

ElhageJ HFD-510, PT Supervisor
PerlsteinR, HFD-510, MO
JohnsonM, HFD-510, CSO

TABLE OF CONTENTS - PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY:.....1

II. SAFETY PHARMACOLOGY:.....1

III. PHARMACOKINETICS/TOXICOKINETICS:.....1

IV. GENERAL TOXICOLOGY:.....3

V. GENETIC TOXICOLOGY:.....11

VI. CARCINOGENICITY:.....11

VII. REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY:.....11

VIII. SPECIAL TOXICOLOGY STUDIES:.....11

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:.....12

X. APPENDIX/ATTACHMENTS:.....12

PHARMACOLOGY/TOXICOLOGY REVIEW

I. PHARMACOLOGY:

Pharmacology conclusions:

B2036-PEG binds specifically to the GH receptor, thereby antagonizing the effects of GH. Hepatic GH receptors from monkey and rabbit demonstrate similar B2036-PEG binding as receptors from human liver while the binding to dog receptors is less. Mouse, and especially rat, demonstrate very little B2036-PEG binding to hepatic GH receptors. Although pharmacological response of rats is less than mice, the renal system in rats more sensitive to chemicals.

When B2036-PEG was administered to mouse at dosages up to 1 mg/kg, no change in IGF-1 concentration was observed. At 2 mg/kg/day for 5 days, an approximately 30% decrease in IGF-1 was seen. In the rabbit, however, IGF-1 concentration fell 25% with a single dose of 3 mg/kg. After multiple doses to the rabbit, IGF-1 concentration decreased up to 80% below baseline. In pregnant rabbits, IGF-1 concentrations appear to decrease during gestation in the absence of any treatment. B2036-PEG administration at 10 mg/kg/day, but not lower, led to a further reduction in IGF-1. In addition, circulating GH concentration in these animals increased, suggesting an increased production of GH in response to absence of feedback inhibition.

In the rhesus monkey, IGF-1 and insulin like growth factor binding protein-3 (IGFBP-3) concentrations decreased after a single IV or SC dose of B2036-PEG at 0.3 or 1 mg/kg. The decrease could be seen 8 hours after compound administration and continued to decrease for 4 days, with suppression continuing through Day 7. Values returned to baseline by Day 14. The extent and duration of the response was dose-dependent. When compound was administered for 14 days at 0.2 mg/kg/day, a decrease in IGF-1 and IGFBP-3 was observed for up to 7 days after the last dose.

II. SAFETY PHARMACOLOGY:

Safety pharmacology conclusions:

Safety pharmacology studies were not conducted. Since growth hormone receptors in rodents have significantly lower affinity to B2036-PEG, the pharmacological effect of B2036-PEG is relatively limited. Administration of B2036-PEG had little effect on IGF-1 levels in mouse and rat. Acute toxicity studies in animals found a significant SC injection site irritation. Similar findings have been noted with other pegylated compounds. The dermal irritability of B2036-PEG was examined in rabbits.

III. PHARMACOKINETICS/TOXICOKINETICS:

PK/TK conclusions:

The binding of pegvisomant to rodent GH receptors is very low compared to other species. In a 4-WK bridging study with pegvisomant manufactured by the new P3 process, the $t_{1/2}$ was 39 ± 12 hrs and drug reached steady state after 5 days in rats. The AUC and C_{max} increased in a dose-proportional manner, however there was 6 to 8 fold drug accumulation with repeated pegvisomant administration (Day 1 vs. Day 28). Contrary to the 6-month rat study (AUC in males $>$ females), the AUC values in females were significantly higher than male rats.

Since the protein part of the B2036-PEG may be degraded similar to compounds synthesized via the previous process, no serious toxicity from metabolism is suspected and lack of specific metabolism studies are less concerning than pegylated portion of B2036-PEG. After degradation of PEG from protein, PEG may go through metabolic pathway similar to ethylene

glycol. Therefore, under chronic conditions, daily injections of B2036-PEG may pose some renal toxicity in subjects with compromised renal function

The PK data from the 4-week rat study bridging the less pure P2 to P3 product is shown in table below. The pegvisomant in serum was assayed by radioimmunoassay. The lower limits of quantification (LLOQ) was

Summary of pharmacokinetic parameters in male and female rats after daily subcutaneous administration of pegvisomant for 28 days.							
	Compound	P3		P3		P2	
	Dose (mg/kg/day)	10		30		30	
Day 1	Parameters	Mean	SD	Mean	SD	Mean	SD
Male	C _{max} (µg/mL)	25	2	69	3	65	12
	AUC _(0-24h) (µg·h/mL)	283	32	726	7	688	152
Female	C _{max} (µg/mL)	46	7	118	21	121	5
	AUC _(0-24h) (µg·h/mL)	521	79	1224	239	1243	42
Day 28	Parameters	Mean	SD	Mean	SD	Mean	SD
Male	C _{max} (µg/mL)	104	35	280	22	242	26
	AUC _(0-24h) (µg·h/mL)	2005	589	6377	366	5254	656
Female	C _{max} (µg/mL)	153	48	440	74	402	104
	AUC _(0-24h) (µg·h/mL)	3118	961	10067	1629	8217	1385

PK Data from 6 month rat study using P2 formulation

Data calculated from plasma B2036-PEG (P2) measured by RIA		3 mg/kg/d		10 mg/kg/d		30 mg/kg/d	
		M	F	M	F	M	F
AUC ₀₋₈ , µg·hr/ml	Day 0	12	18	36	58	116	160
	Day 90	277	455	945	1146	3820	2753
	Day 178	316	470	1671	1561	5142	3496
C _{max} , µg/ml	Day 0	3.94	4.52	9.49	14.9	28.6	42.5
	Day 90	43.4	73.9	166	166	662	422
	Day 178	60.8	65.8	268	218	709	471

Impurities in different manufacturing of B2036 products:

Product	Percent product ingredients	
	P3	Pharmacia
B2036 (Main drug)		

IV. GENERAL TOXICOLOGY:

Study title: Four-Week subcutaneous toxicity study in rats (P2 and P3 material).

Key study findings: There were no significant differences in the toxicity profile of the P2 formulation compared to new the P3 formulation.

Study no: 2002-0198

Volume #, and page #: 1, page 1-303

Conducting laboratory and location: Pharmacia

Date of study initiation: May 03, 2002

GLP compliance: yes

QA report: yes (x) no ()

Drug, lot #, radiolabel, and % purity: P3 product, 886153A, nonlabeled, 95% purity
P2 product, SP17447, nonlabeled, <87% purity

Formulation/vehicle: Glycine (1.36 mg), mannitol (36 g), sodium phosphate dibasic anhydrous (1.04 mg), sodium phosphate monobasic monohydrate (0.36 mg) and water (2 ml).

Methods: The objective of this 1-month rat study was to bridge the P2 product manufactured by Abbott with <87% purity to new product manufactured by Pharmacia with 95% purity. Two doses of P3 were compared to maximum dose of P2 (30 mg/kg/d) used in 6-month rat study. Drug solutions were prepared daily prior to use from freeze dried pegvisomant (20 mg/vial). The solution concentrations were measure at the beginning and at the end of the study. The dose solution concentrations for P2 (30 mg/kg/d) and P3 solutions for the 10 and 30 mg/kg/d doses were outside the $\pm 15\%$ acceptable range (see table). Less drug may have been delivered to rats, although the AUC data suggests rats had higher exposure during this study than in the 6 month rat toxicity study (see page 6).

Concentration of drug product used in 1-month rat bridging study

Samples	Date	Intended Conc., mg/ml	Measured Conc., mg/ml	% change
P2, 30 mg/kg/d	5/09/02	10	10.356	+ 3.5%
P2, 30 mg/kg/d	6/06/02	10	8.06	- 20%
P3, 30 mg/kg/d	5/09/02	10	9.627	+ 3.7%
P3, 10 mg/kg/d	5/09/02	3.33	2.631	- 21%
P3, 30 mg/kg/d	6/06/02	10	7.934	- 21%
P3, 10 mg/kg/d	6/06/02	3.33	2.773	-16.7%

Dosing:

Species/strain: SD rats,

#/sex/group or time point (main study): 10/sex/dose

Satellite groups used for toxicokinetics or recovery: 3/sex/dose

Age: 7 Wks old

Weight: 182-238 g M, 157-182 g F

Doses in administered units: not applicable

Route and volume: SC, 3 ml/kg

Observations and times:

Clinical signs: twice a day

Body weights: twice a week

Food consumption: once a week

Ophthalmoscopy: pre-test and on Day 26

EKG: not applicable

Hematology: standard hematology on Day 28, however, due to technical problems, RBC, MCV, Hgb were not measured. The missing data was unlikely to have any consequence in safety analysis. The slight increase in Hgb (6.7%) noted at 30 mg/kg/d with P2 product in the 6 month rat study was non-consequential.

Clinical chemistry: standard chemistry on Day 28

Urinalysis: On day 28, animals were given 10 ml/kg of water and fasted for 16 hr (food only). Urine was collected over the fasting period.

Gross pathology: Day 29, all animals

Organs weighed: See page 12

Histopathology: Tissues from control and HD were evaluated. Several suspect tissues were also examined in LD group (injection sites, mandibular and mesenteric lymph nodes, inguinal skin and kidneys, See page 12 for list of tissues, examined in control and HD animals.

Toxicokinetics: PK samples were collected on Day 1 (at 0, 6 and 24 hr), before daily dose on Day 5, 14 and 21 and on Day 28 (0, 6, 24, 48, 96, 120 and 144 hr post dose). Plasma concentration of pegvisomant was measured by a validated radioimmunoassay.

Statistical Analysis: Statistics for males and females were done separately. The homogeneity of variance was carried out by Bartlett's test. Fisher's test and Dunnett's test were used for normally distributed data. Cochran and Cox's test were used for non-homogenous or categorical data.

Results:

Mortality: none

Clinical signs: No drug related clinical signs were noted. Alopecia was noted in a few control and HD males.

Body weights: No significant difference between P2 and P3 and controls.

Food consumption: No significant difference between P2 and P3 and controls

Ophthalmoscopy: No abnormalities

Hematology:

- No difference between P2 and P3 animals.
- A decrease in lymphocytes and white blood cells noted with both P2 and P3 product at 30 mg/kg/d. Similar findings were also observed in the 6-month rat study with P2 at 30 mg/kg/d.
- An increase in eosinophils in males at HD was observed.

Hematology parameters

Hematology parameters	Sex	Percent change, %		
		P3, 10 mg/kg/d	P3, 30 mg/kg/d	P2, 30 mg/kg/d
White BC	M		-18%	-18
	F		-25%	-39%
Lymphocytes	M		-23%	-21%
	F		-26%	-41%
Eosinophils	M		31%	31%

Clinical chemistry:

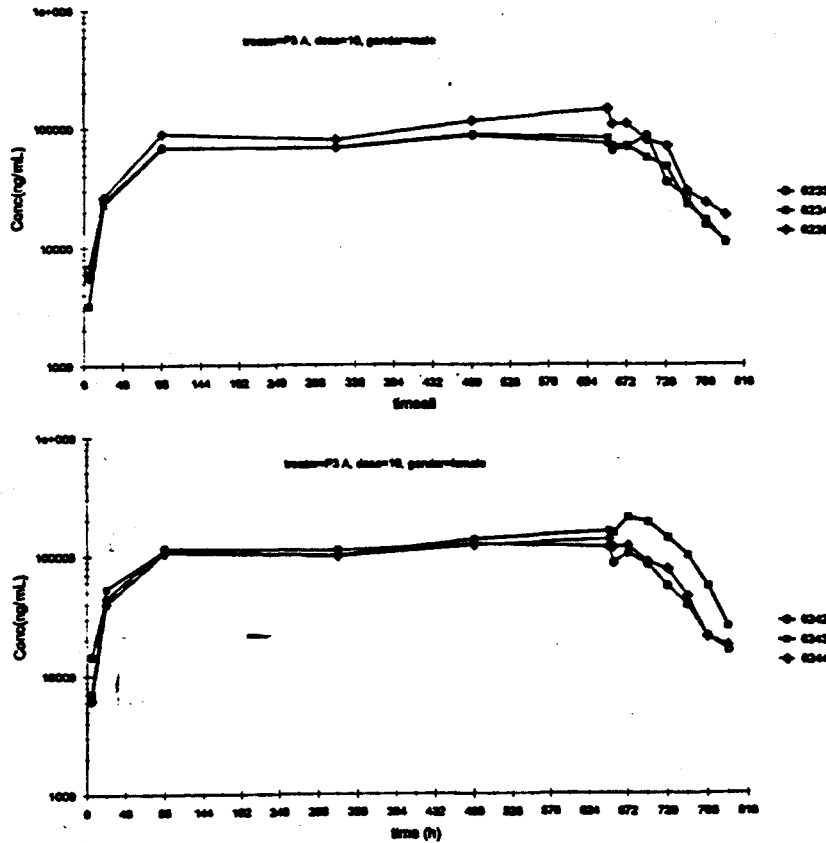
- No difference between P2 and P3.
- There was a slight increase in triglycerides and total cholesterol in males treated with 10 and 30 mg/kg/d P3 or 30 mg/kg/d P2 relative to controls.
- Slight decrease in alkaline phosphatase in at 30 mg/kg/d P2 and P3 product. The significance of this is not clear.
- Slight but significant decrease in creatine kinase was noted in P2 treated rats.

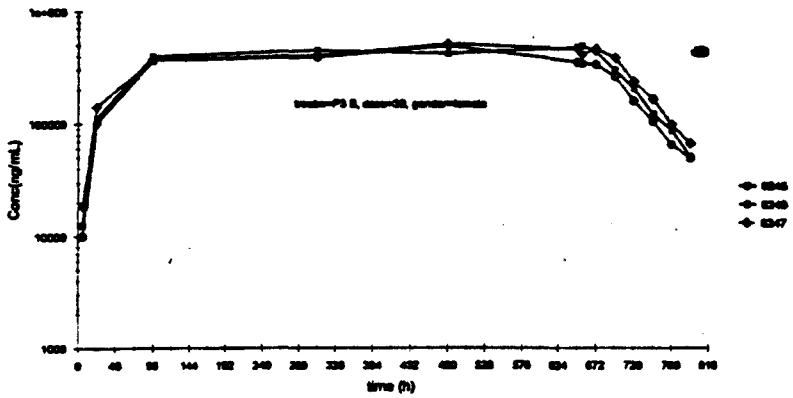
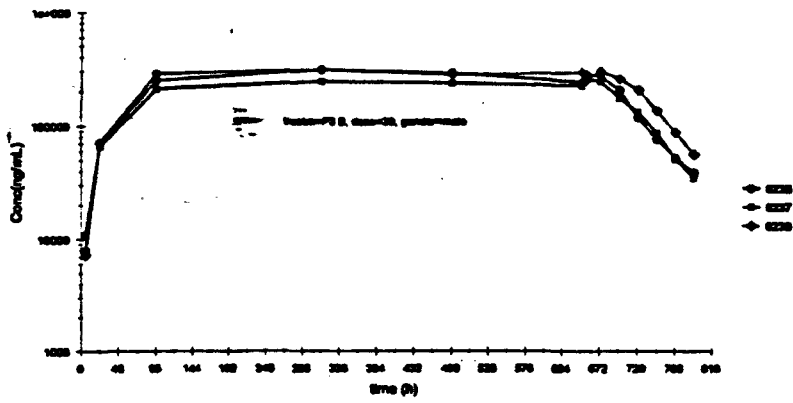
Toxicokinetics:

- AUC and C_{max} values increased in a dose proportional manner on both Day 1 and Day 28 for the P3 product. The AUC and C_{max} for P2 and P3 at 30 mg/kg/d appeared to be similar.
- Repeated administration increased AUC_{0-24} by 6 to 8 fold from Day 1 to Day 28.
- Drug appeared to reach steady state by Day 5.
- The $t_{1/2}$ was 39 hrs in rats
- Drug exposure was about 30% greater in females than males. Greater drug exposure in females may explain some of the renal findings noted at 30 mg/kg/d in P3 treated females.

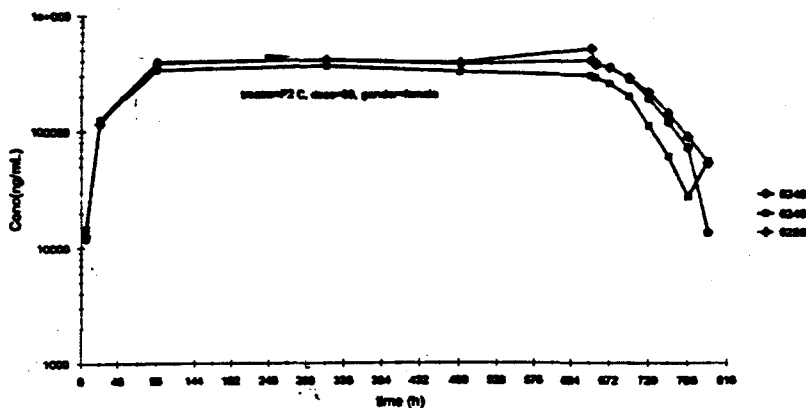
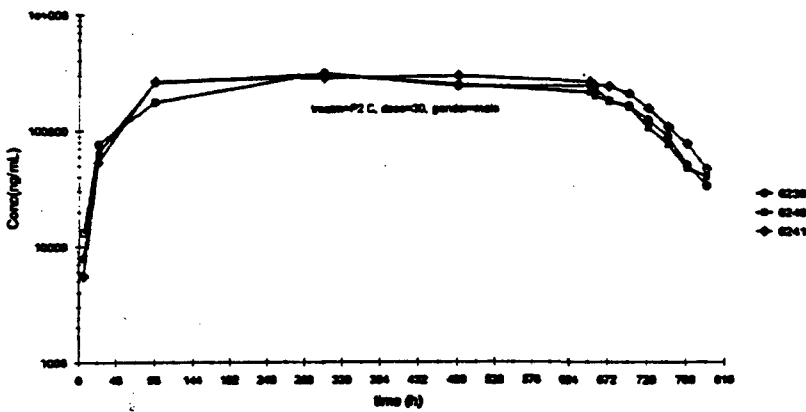
Compound		10 mg/kg/d P3	30 mg/kg/d P3	30 mg/kg/d P2
Day 1 Male	C_{max} μ g/ml	25	69	65
	AUC_{0-24} μ g.h/ml	283	726	688
Day 1 Female	C_{max} μ g/ml	46	118	121
	AUC_{0-24} μ g.h/ml	521	1224	1243
Day 28 Male	C_{max} μ g/ml	104	280	242
	AUC_{0-24} μ g.h/ml	2005	6377	5254
Day 28 Female	C_{max} μ g/ml	153	440	402
	AUC_{0-24} μ g.h/ml	3118	10067	8217

Plasma concentration profile of P3 (10 and 30 mg/kg/d) in rats





Plasma profile of P2 (30 mg/kg/d) in rats



The AUC₀₋₉₆ in humans after 20 mg/dose (0.333 mg/kg) was 207.8 µg.h/ml. The 30 mg/kg/d in rats is approximately 31 to 48 human therapeutic dose of 20 mg/day, based on AUC.

Species	Dose, mg/kg/d	AUC ₀₋₂₄ , µg.hr/ml	Ratio of Animal to Human AUC
4 Wk bridging Study	10 (P3)	2005 M, 3118 F	10 M, 15 F
	30 (P3)	6377 M, 10067 F	31 M, 48 F
	30 (P2)	5254 M, 8217 F	25 M, 39 F
Human dose, 20 mg /d		207.8 (AUC _{0-inf})	

Summary of individual study findings:

- There were no deaths and no notable change in clinical signs, body weights, food consumption and ophthalmoscopy findings. Alopecia was noted in all rats.
- Significant decrease in white blood cells and lymphocytes were noted in P2 and HD P3
- Significant increase in eosinophils in P2 and HD P3
- A moderate increase in triglycerides and total cholesterol occurred in P2 and P3 treated males and slight decrease in ALP in P2 and HD P3 treated rats
- Increases of both absolute adrenal weights in males of all treated groups without histological findings. This was also observed in 6 month rat study.
- Dose-dependent local inflammatory reactions at the injection sites with P3 (10 and 30 mg/kg/day) and P2 material (30 mg/kg/day).
- Presence of vacuolated macrophages at the injection site in the subcutaneous tissue. Small numbers of vacuolated macrophages were also noted in some lymph nodes from the groups treated with pegvisomant.
- No substantial differences in the incidence or severity of injection site findings between HD P3 and P2
- 1 HD P3 female had minimal renal cortical tubular vacuolation
- 1 HD male had marked testicular atrophy.
- Both AUC and C_{max} values increased in a dose proportional manner.
- Systemic exposure (AUC) at Day 28 was higher than at Day 1 (accumulation ratio 6-8). Drug exposure was about 30% higher in females than males for all treated groups contrary to 6 month rat study.
- The steady-state conditions were reached after 5 days of treatment, with t_{1/2} of 39±12 hrs.
- No differences in C_{max} and AUC values of P2 and P3 product.
- The 30 mg/kg/d dose of P3 produced exposure multiples in rats of 31 to 48 times AUC exposure obtained with the human therapeutic dose of 20 mg/day.
- Overall, there were no differences in toxicological profile of the subcutaneous P3 and P2 products in rats.

Toxicology conclusions:

In this 4-WK bridging study, the sponsor had compared the maximum dose of P2 (30 mg/kg/d, SC) used in the 6-month toxicity study to the new P3 product (10 and 30 mg/kg/d, SC) in SD rats.

The major findings were consistent with the 6 month rat study: inflammation at the injection site with minor decreases in lymphocytes and white blood cells with both 30 mg/kg/d P2 and P3 product. The injection site inflammations were dose dependent, more prominent in males and clearly drug related. There was no clear evidence to support or dismiss renal findings noted in the 6-month rat study. However, there was one incidence of minimal renal cortical tubular

vacuolation in a 30 mg/kg/d P3 treated female. One high dose male had marked testicular atrophy. The increase in adrenal gland weight noted in the 6-month study was also observed with both doses of P3 and P2. The concerns regarding potential for renal toxicity will be clarified with the 2-year bioassay to be conducted as a phase IV requirement.

The AUC values in both male and female rats increased by 6 to 8 fold from day 1 to day 28. The females had significantly greater drug exposure than males contrary to observation in the 6-month rat study. The 30 mg/kg/d P3 produced exposures 31 to 48 fold greater than therapeutic AUC exposures with the human daily dose of 20 mg/day.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

V. GENETIC TOXICOLOGY:

Genetic toxicology conclusions:

Sponsor had carried out only two genotoxicity test: Ames and Chromosomal aberration test. The Ames test was reviewed by Ron Steigerwalt. Under the test conditions, B2036-PEG did not cause reverse mutation of Salmonella or E.coli (negative Ames test). The chromosomal aberration test was also negative

Labeling recommendations: Pegvisomant was not mutagenic in the Ames assay or clastogenic in the in vitro chromosomal aberration test in human lymphocytes. Labeling recommendation was made in the full NDA review and has not been changed.

VIII. SPECIAL TOXICOLOGY STUDIES: None

IX. DETAILED CONCLUSIONS AND RECOMMENDATIONS:

Conclusions:

Overall there appeared to be no notable differences in toxicological profile of new P3 and old P2 products.

General Toxicology Issues:

The single 2-year bioassay required as part of phase IV development, should clearly demonstrate any possible renal toxicity concerns with pegvisomant, a pegylated growth hormone antagonist

Recommendations:

A 2-year carcinogenicity study in rodents should be submitted as part of phase IV development plans. The protocol for carcinogenicity dose selection should be submitted for review by Executive Carcinogenicity Assessment Committee.

X. APPENDIX/ATTACHMENTS:

Addendum to review: none

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

/s/

Fred Alavi

12/13/02 03:47:37 PM

PHARMACOLOGIST

4-WK rat bridging study to compare new P3 product
manufactured by pharmacia to P2 product by

4-WK rat bridging study

Jeri El Hage

12/13/02 04:28:07 PM

PHARMACOLOGIST

7/9/01

MEMORANDUM

DATE: June 18, 2001

FROM: Kenneth L. Hastings, Dr.P.H.
Acting Associate Director for Pharmacology/Toxicology, ODE II

TO: NDA 21-106
Somavert (pegvisomant) injection

I have reviewed the information supplied in the action package for this drug product and agree that the NDA is approvable. Specifically, the sponsor should complete a six-month non-rodent toxicity study and a rabbit teratology (segment II) study with the marketed drug product as recommended by the Pharmacology/Toxicology reviewer, Dr. Fred Alavi. The reason given for this recommendation is that the marketed product is significantly less pure than the drug substance used in non-clinical toxicology studies. I concur with the reviewer's request. Also, the reviewer requests that two year rodent carcinogenicity studies should be conducted as a Phase 4 commitment, which is reasonable given that this product will be administered chronically.

There are two items that I suggest should be amended in the final action letter. On page 6, the first item under Pharmacology/Toxicology: substitute "should" for "must". If the sponsor improves the manufacturing of the drug such that the level of impurities in the final product is comparable to those in the test article used in submitted non-clinical toxicology studies, conduct of this study might not be necessary. Also, under the second Pharmacology/Toxicology section, the request for monitoring renal function in acromegalic patients should be incorporated into the Clinical section since this is not a nonclinical issue.

/S/

Kenneth L. Hastings, Dr.P.H.

**APPEARS THIS WAY
ON ORIGINAL**

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

/s/

Kenneth Hastings
7/9/01 01:04:31 PM
PHARMACOLOGIST

Team Leader Memo

To: NDA 21-106 /Somavert/Sensus-Pharmacia and Upjohn

From: Karen Davis-Bruno; Ph.D.; Supervisory Pharmacologist; DMEDP, HFD-510

Date: 6/25/01

Re: Carcinogenicity assessment

Meeting minutes from May 22, 1998 indicate that a rat two year carcinogenicity bioassay was considered acceptable by DMEDP. Acceptance of a single two year carcinogenicity bioassay as a post-marketing (Phase 4) commitment is contingent upon negative study results from a valid study. Somavert represents a significantly improved therapy for the serious/life threatening indication of acromegaly and therefore it is reasonable to request a two year rodent carcinogenicity study as a Phase 4 commitment given this product will be administered chronically.

/S/

, 6/25/01

Karen Davis-Bruno; Ph.D.

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Karen Davis-Bruno

6/25/01 11:29:03 AM

PHARMACOLOGIST

clarification of Phase 4 rat 2yr. bioassay

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA number: 21-106

Review number: 01

Serial number/date/type of submission: 000/Dec 16, 1999/ NDA, Orphan Drug

Information to sponsor: Yes (X) No ()

Sponsor and/or agent: Sensus Drug Development Corp., 98 San Jacinto Blvd., Suite 430, Austin, TX 78701, Pharmacia, Kalamazoo, MI as of 2/2001

Manufacturer for drug substance: B2036-PEG was originally manufactured by Genentech. Later, sponsor switched manufacturer to _____
Pharmacia Upjohn (Kalamazoo, MI) recently acquired Sensus (2/29/2001). Abbot Laboratories will be the future manufacturer of the drug product.

Reviewer name: Fred K. Alavi, Ph.D. Pharmacology/Toxicology reviewer

Division name: Department of Metabolism and Endocrine Drug Products, HFD 510

Review completion date: April 26, 2001

Drug:

Trade name: Somavert ®

Generic name: pegvisomant, rhGH antagonist (PEGylated)

Code name: B2036-PEG

Chemical name:

CAS registry number:

Mole file number:

Molecular formula/molecular weight: B2036-PEG is a 191 amino acid polypeptide with two disulfide bonds. As an analogue of human GH, it contains nine substitutions in the first and third α -helices. There are 4-5 PEG moieties (~5000 Dalton each) covalently bound to amino groups on the surface of the molecules. This increases its mass to 42-46,000Da.

Relevant INDs/NDAs/DMFs: IND _____ and IND _____ (for diabetes indication)

Drug class: GH antagonist, pegylated

Indication: Acromegaly (third line treatment)

Clinical formulation: Per vial:

10 mg B2036 protein (white lyophilized powder stable for 6 months at 2-8°C)

36 mg Mannitol

1.36 mg glycine

0.01M sodium phosphate, pH 7.4

To be reconstituted in water up to 10 mg/ml

Route of administration: SC daily

Proposed use: For treatment of acromegaly

Disclaimer: use of sponsor's material: Use of sponsor's material was restricted to the molecular structure and PK/TK and other data tables. Scanned tables pasted as images in the review can be easily recognized by their appearance in the review. Some of the introductory text that was found to represent the drug background accurately were modified and incorporated into the INTRODUCTION section.

OVERALL SUMMARY AND EVALUATION:

Introduction:

B2036-PEG (pegvisomant, Trovert®, Somavert®) is a recombinant human growth hormone (hGH) receptor antagonist to which polyethylene glycol has been attached. B2036-PEG is being developed for the treatment of acromegaly. Acromegaly is chronic, debilitating disorder resulting from excessive secretion of growth hormone (GH) by non-malignant pituitary adenoma. The total number of acromegalic patients in the US, Europe and Japan is estimated to be about 40,000 patients.

This compound has significant structural similarities to the recombinant human growth hormones somatrem (Protopin®) and somatropin (Nutropin®). A total of nine mutations were made within the first and third α -helix of the 191 amino acid molecule to alter the binding characteristics of the molecule with human growth hormone (hGH) receptor sites 1 and 2. The protein was then pegylated, that is, covalently bound to 4-5 polyethylene glycol (PEG) molecules. PEGylation increases the size of the molecule, thereby increasing its half-life in vivo and reducing the likelihood of antibody formation to the molecule during administration to humans. The molecular weight of the PEG was approximately 5000.

Safety evaluation:

The sponsor has switched from the initially proposed weekly dosing to daily dosing. Due to lack of consistency in data collection, safety margins were calculated by several methods. In the table below, exposure ratios (ER) were using AUC and dosage based on body surface area for NOAEL.

Species	NOAEL	AUC ₀₋₉₆ , µg.hr/ml	Ratio of Animal to Human AUC	mg/m ²	Ratio of Animal NOAEL to maximal Human dose, mg/m ²
26-Week Monkey	0.042 mg/kg/d	116	0.6	0.5	0.04
Rabbits Reprotox, Day 0-7 or Day 7-21	3 mg/kg/d			36	3
26-Week Rat study	10 M 3 F	—	—	60 M 18 F	5 (Males) 1.5 (Females)
Human dose, 20 mg = 0.333 mg/kg for a 60 kg	—	207.8 (AUC _{0-inf})		12	

Plasma concentrations of B2036-PEG in 6-month rat study were measured up to 8 hrs. Since plasma B2036-PEG were inconsistent and not dependable, AUC comparisons of a human to rat ratio was not calculated. In addition sponsor was unable to obtain steady state bioavailability data after single dose SC or IV administrations, thus used an exposure ratios (ER) based C_{max} values. Although this may be one alternative, this review describes interspecies dose comparisons primarily based on mg/m².

In the 26-week monkey study, animals were treated once a week at doses of 0.3, 1 and 3 mg/kg. Since in humans B2036-PEG is indicated for daily SC dosing of acromegalic patients, the 6-month monkey study is invalid. In addition, doses used were relatively low. ICH guidelines require the frequency of dosing in animal toxicity studies to match proposed clinical dosing regimen with minimum 10-fold safety factor. With NOAEL of 0.3 mg/kg/wk, the daily dose is about 0.043 mg/kg/day. The safety margin for the maximal human dose of 20 mg/day based on AUC or body surface area were less than one (no safety margin). The safety margins were used for informative purposes, since rodents do not respond to pharmacological effects of B2036-PEG except at very high concentrations. In monkeys, B2036-PEG binds to GH receptor thus causing significant decrease in IGF-1 levels in monkeys. Since plasma concentrations of GH and IGF-1 levels in healthy monkeys are normal vs. acromegalic patients (excessive GH and IGF-1), excessive

inhibition of IGF-1 levels in healthy monkeys may cause a secondary toxicity not likely to be seen in acromegalic patients.

In the 6-month rat study, animals were treated daily with SC injection of B2036-PEG (3, 10 and 30 mg/kg/day). Since rats do not respond to pharmacological effects of B2036-PEG, only the non-pharmacological toxicity of B2036-PEG is observed. Although the exposure ratio of maximal human dose to rat NOAEL doses (mg/m²) were better than those in monkeys, they were still low, 2 to 5 fold.

Standard safety toxicity studies for cardiovascular, pulmonary, renal and neurological effects were not carried out. There is clear evidence that PEGylation of the active compound; B2036 was associated with renal toxicity in 6-month rat toxicity study. Sponsor has argued in the past that rats do not respond to B2036-PEG and therefore may not serve as a good model. This reviewer believes that rats can demonstrate the intrinsic toxicity of B2036-PEG. Until an acromegalic animal model with elevated IGF-1 is available, rats may help to differentiate the intrinsic toxicity of B2036-PEG from toxicity secondary to B2036-PEG induced abnormally low IGF-1 levels.

Other Safety related issues:

For the acromegaly indication, the use of the rabbit as a single species in the reproductive toxicity studies was considered sufficient by the CDER Reprotoxicity Committee due to the absence of pharmacological response in the rat. In segment I and II studies in rabbits, B2036-PEG was not teratogenic. There was a small increase in postimplantation loss at 10 mg/kg/day, approximately 10 time human exposure. No other serious toxicities were noted.

In the 6-month toxicity study in rats, doses higher than 3 mg/kg/d in females and 10 mg/kg/day in males significantly increased proteinuria. Histological evaluation of kidney tissue found nephropathy in female rats at 30 mg/kg/d (HD). Proteinuria persisted during recovery period in both males and females especially at HD, suggesting that renal damage during treatment persisted even during the recovery period.

Sponsor has not completed the standard 2-year rodent bioassays. The agency had agreed to the submission of carcinogenicity study during phase IV. The sponsor has submitted several in vitro and in vivo (non-GLP) mutagenicity studies in growth hormone responsive cells lines to support conducting full carcinogenicity post-approval. In these studies, B2036-PEG was given to mice bearing human meningioma tumors, 4 lines of human breast tumors and murine colon tumors. In these studies, B2036-PEG did not propagate tumor growth and in some cases appeared to decrease growth rate or lower rate of metastasis.

Conclusions:

B2036-PEG is a human GH antagonist that actively binds to monkey and rabbit GH receptor with very low affinity to rat or mice GH receptors. Several short and two 6-month toxicity studies in monkey and rats were submitted. In the 6-month monkey study, animals were treated once a week, therefore this study is insufficient to support the safety of the daily dosing regimen in humans. The NOAEL dose (0.3 mg/kg/wk) in 6 month monkey study provided no safety margin to maximal human dose. Overall the toxicological findings were slight and tended to be inconsistent. This may be a reflection of the low multiples of exposure. However, there were some hematologic and blood chemistry effects that were consistent (decreased Hb, RBC, some decrease in APTT and a decrease in ALP). These slight changes were detected in both species although rodents were supposedly not physiologically responsive to the growth hormone antagonist, B2036-PEG. A slight decrease in body weight was noted in acute studies in mice and in monkeys. While this might be expected in monkeys due to the activity of the compound, it is not clear why this occurred in mice, which are presumably unresponsive. Also noted were increases in total protein and albumin. There were slight injection site reactions noted in both species.

The 6-month rat study had provided a safety ratio of 2 to 5 times human exposure based body surface area. At doses greater than 3 mg/kg/day in females (2 X) and 10 mg/kg/day (5X human exposure, mg/m²), B2036-PEG caused proteinuria. At approximately 15 times human exposure levels based on mg/m², nephropathy was noted in female rats (30 mg/kg/d) at the end of week 26. No renal findings were reported in other studies. This may be due to the fact that the duration and dosage of B2036-PEG were small. The renal findings are most likely due to the PEG covalently bonded to B2036. This may not pose any threat to healthy acromegalic patients but in individuals with reduced renal function, the impact of repeated administration of B2036-PEG should not be ignored. The proteinuria was noted even after 4-week recovery period, suggesting renal damage persisted even after treatment was terminated. B2036-PEG was not mutagenic in standard battery or teratogenic in rabbit reprotoxicity studies. Pregnant rabbits appeared to have greater post-implantation loss at the highest dosage level (10 mg/kg, 10 times human exposure based upon body surface area).

Communication review:

RECOMMENDATIONS:

Internal comments:

- Recommendation, Approvable/non-approval (?) pending completion of a valid 6-month non-rodent study and a rabbit teratology study with the final drug product. All the toxicology studies except the 6-month rat study (SEN-118) were conducted with the product produced by Genentech, which was 95% pure. The product manufactured by _____ has only 55-75% purity (as per chemist). Therefore, the studies recommended below should be conducted utilizing the to-be-marketed drug product.
- Sponsor must conduct a 6-month non-rodent toxicity study with daily administration of the clinical formulation. Since the drug product is covalently bonded to PEG, an additional control group with PEG-5000 (10 to 25X human dose) is recommended.
- Recommend a repeat of the rabbit teratology study with at least one dose high enough to produce signs of maternal toxicity in rabbits.
- A two-year carcinogenicity must be completed as a Phase IV commitment.
- A phase IV study monitoring renal function in acromegalic patients should be considered to assess the renal effects of chronic daily dosing with the pegylated compound.

External recommendations (to sponsor):

Draft letter content for sponsor (if not same as above):

- Sponsor must conduct a 6-month non-rodent toxicity study with daily administration of the clinical formulation. Since the drug product is covalently bonded to PEG, an additional control group with PEG-5000 (10 to 25X human dose) is recommended.
- Sponsor should conduct a rabbit teratology study with at least one dose high enough to produce signs of maternal toxicity in rabbits and to-be-marketed drug product.
- The sponsor should submit a protocol for a 2-year rodent carcinogenicity study for review by the Executive Carcinogenicity Assessment Committee prior to initiation of the study. The sponsor must conduct a carcinogenicity study as a Phase IV commitment.
- A phase IV study monitoring renal function in acromegalic patients should be considered to assess the renal effects of chronic daily dosing of pegylated compound.

Future development or issues:

- Sponsor must conduct a 6-month non-rodent toxicity study with daily administration of the final clinical formulation. Since the drug product is covalently bonded to PEG, an additional control group with PEG-5000 (10 to 25X human dose) is recommended.
- A two-year carcinogenicity in rats should be completed as a Phase IV commitment.

Recommendation: Non-approval until valid 6-month non-rodent study and rabbit teratology studies are completed.

/S/

Fred K. Alavi, Ph.D.
Pharmacology Reviewer

/S/

Jeri El Hage, Ph.D.
Pharmacology Supervisor

cc: IND Arch
HFD510
HFD510/Alavi/Elhage/Perlstien/King
Review Code: NA
Filename: NDA 21-106.000.doc

Memorandum of non-concurrence (if appropriate, attached):

Studies reviewed within this submission: Please see first table of content on Page 6 for list of studies reviewed for this NDA.

Studies not reviewed within this submission: Please see second table of content on page 52, studies reviewed by Ron Steigerwalt.

Table of Contents

Content	Page
Introduction and drug history	<u>7</u>
Pharmacology	<u>8</u>
Safety Pharmacology	<u>10</u>
Binding of B2036-PEG to liver growth hormone receptor (SEN-209)	
Pharmacokinetics and Toxicokinetics	<u>12</u>
Toxicology Studies	
A 6-month subcutaneous toxicity study of B2036-PEG in rats	<u>18</u>
Addendum	<u>29</u>
Genotoxicity studies	
Structural chromosomal aberration assay in human lymphocytes with B2036	<u>30</u>
Mutagenicity test	
The effect of B2036-PEG on human meningioma growth in vitro (SEN-206)	<u>34</u>
The effect of B2036-PEG on beast cancer cell lines	<u>35</u>
Therapy of experimental liver metastases produced by murine CT-26 colon carcinoma with irinotecan (topoisomerase I inhibitor) with or without B2036-PEG (SEN-207)	
Reprotoxicity	
A study of the effects of B2036-PEG administered subcutaneously on early embryonic development to implantation in rabbits (SEN-120)	<u>39</u>
A study of the effects of B2036-PEG administered subcutaneously on embryo/fetal development in rabbits (SEN-119)	<u>43</u>
Toxicology Conclusion	<u>50</u>
Appendix (studies reviewed By Ron Steigerwalt)	<u>52</u>

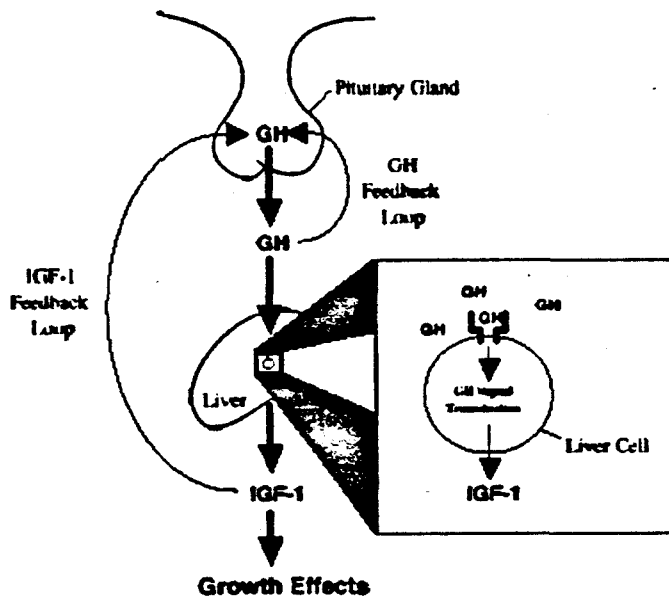
Abbreviations: low dose (LD), mid dose (MD), high dose (HD), hemoglobin (Hgb), red blood cell (RBC), human growth hormone (hGH), insulin like growth actor-I (IGF-1), packed cell volume, no adverse effect level (NOAEL), alkaline phosphatase (ALK), blood urea nitrogen (BUN), polyethylene glycol (PEG).

Introduction and drug history:

Introduction:

B2036-PEG (pegvisomant, Trovert®, Somavert®) is a recombinant human growth hormone (hGH) receptor antagonist to which polyethylene glycol has been attached. B2036-PEG is being developed for the treatment of acromegaly. Acromegaly is chronic, debilitating disorder resulting from excessive secretion of growth hormone (GH) by non-malignant pituitary adenoma. The total number of acromegalic patients in the US, Europe and Japan is estimated to be about 40,000 patients.

This compound has significant structural similarities to the recombinant human growth hormones somatrem (Protopin®) and somatropin (Nutropin®). A total of nine mutations were made within the first and third α -helix of the 191 amino acid molecule to alter the binding characteristics of the molecule with human growth hormone (hGH) receptor sites 1 and 2. The protein was then pegylated, that is, covalently bound to 4-5 polyethylene glycol (PEG) molecules. PEGylation increases the size of the molecule, thereby increasing its half-life in vivo and reducing the likelihood of antibody formation to the molecule during administration to humans. The molecular weight of each PEG was approximately 5000.



THE GROWTH HORMONE AND IGF-1 AXIS

The liver is the major site of the IGF-1 synthesis. Binding of IGF-1 to IGF type I receptors stimulates tyrosine kinase activity and autophosphorylation of tyrosine molecule, which produces cell differentiation or division (or both). IGF is considered a progression factor. A cell that has reached G1 phase, under IGF-1 exposure, undergoes division in the S phase of the cell cycle. Other functions attributed to IGF-1 include stimulatory effect on cartilage growth, hematopoiesis, ovarian steroidogenesis, myoblast proliferation and differentiation.