CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-106

Administrative Documents

Time Sensitive Patent Information
Pursuant to 21 U.S.C. 355 for
Somavert™ (pegvisomant)

NDA 21-106

The following is provided in accordance with the Drug Price Competition and Patent Term Restoration Act of 1984:

Trade Name:	Somavert™
Generic Name:	pegvisomant
NDA Number:	21-106
Approval Date:	Pending

U.S. Patent 5,849,535

Expiration Date:	*September 21, 2015*
Type of Patent:	Drug, Drug Product and Method of Use
Name of Patent Owner:	Genentech, Inc.
Relationship of Applicant:	Sensus Drug Development Corporation has an exclusive license to this patent for the subject of the application for which approval is being sought.

The undersigned declares that U.S. Patent Number 5,849,535 covers the active ingredient of Somavert. This product is the subject of the application for which approval is being sought.

September 20, 1999

Name: William F. Bennett, Ph.D.
Title: Senior Vice President

EXCLUSIVITY SUMMARY for NDA # 21-106 SUPPL # _____

Trade Name Somavert Generic Name pegvisomant for injection

Applicant Name Pharmacia & Upjohn HFD- 510

Approval Date _____

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/_X_/ NO /___/

   b) Is it an effectiveness supplement? YES /___/ NO /_X_/

      If yes, what type(SE1, SE2, etc.)? _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X_/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      _____

      _____

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

      _____

      _____

d) Did the applicant request exclusivity?

YES /___/ NO /_x_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_x_/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X_/

If yes, NDA # _____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /_X_/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

NOT APPLICABLE

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /___/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /___/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /___/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /___/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /___/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study # _____
NDA # _____ Study # _____
NDA # _____ Study # _____

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /___/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study # _____

NDA # _____ Study # _____

NDA # _____ Study # _____

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # _____

Investigation #__, Study # _____

Investigation #__, Study # _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____
	_____
Investigation #2	
IND # _____ YES /___/	NO /___/ Explain: _____
	_____
	_____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____
Investigation #2	
YES /___/ Explain _____	NO /___/ Explain _____
_____	_____
_____	_____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /___/

If yes, explain: _____

_____

_____

Prepared by:

{See appended electronic signature}
Enid Galliers
Chief, Project Management Staff
DMEDP, ODE II, OND, CDER

Concurred by:

{See appended electronic signature}
Robert J. Meyer, M.D.
Director
Office of Drug Evaluation II
OND, CDER

c:
Archival NDA
HFD- /RPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

Robert Meyer
3/17/03 12:33:09 PM

AUG 29 2002

DEBARMENT CERTIFICATION FOR
SOMAVERT® (pegvisomant for injection)

Pursuant to section 306(k)(1) of the Federal Food, Drug and Cosmetic Act, the applicant certifies that, the applicant did not and will not use in any capacity the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act in connection with this application.

Satish C. Tripathi
Director
Global Regulatory Affairs, New Drugs

08/29/2002
Date

B2036-PEG (pegvisomant)

NDA 21-106

DEBARMENT CERTIFICATION

In accordance with the certification provision of the Generic Drug Enforcement Act of 1992 as outlined in correspondence dated 29 July 1992, from Daniel L. Michels, Office of Compliance, Sensus Drug Development Corporation hereby certifies that to the best of its knowledge and belief, it did not and will not use in any capacity the services of any person debarred under section 306 (a) or (b) of the Generic Drug Enforcement Act of 1992 in connection with this application.

Mike Bernstein

Mike Bernstein, M.P.H.
Senior Director, Regulatory Affairs

17 June 1999

Date

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research

DATE: March 25, 2003

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-106
Somavert (pegvisomant) injection
Pharmacia and Upjohn
Treatment of acromegaly

SUBJECT: Division Director memo related to repeat tradename review

Background

DMETS has conducted a second review of the proprietary name, Somavert, in light of substantial elapsed time since their original March 21, 2001 review and the imminent approval of this NME for the treatment of acromegaly.

The principal look-alike/sound-alike comparisons potentially leading to confusion and medication errors are:

1. Somatrem (growth hormone injection)
2. Somatropin (growth hormone injection)
3. somatostatin analogue (Sandostatin-octreotide acetate for injection).

The division has previously commented on the concerns of DMETS and continues to find the tradename Somavert acceptable for the following reasons:

1. The growth hormone products listed are for the treatment of children with growth hormone deficiency and resultant short stature. Somavert is for the treatment of adults with acromegaly to block the effects of growth hormone and thus obviate the sequelae of growth hormone excess. The efficacy of intervention with both growth hormone and pegvisomant is monitored in ongoing fashion as part of standard of care of patients with the respective target diseases. These drugs obviously possess diametrically opposite pharmacologic activities, but the short-term consequences (leading up to an interval monitoring visit) of treatment with the wrong product are not serious.
2. With regard to potential confusion with Sandostatin (chemical name: octreotide), there seems likewise little to no risk of short term treatment with the wrong drug. Indeed, both Somavert and Sandostatin are intended for the treatment of acromegaly, and Sandostatin is itself a highly effective treatment. As above, response is monitored periodically in the treatment of acromegaly, so that failure to control GH and/or IGF-1 levels will lead,

regardless of the prescribed, dispensed, or administered treatment, to dose adjustment and/or alternative therapies.

Finally, and in sum, acromegaly (as is growth hormone deficiency) is a disease treated by specialists, and involves careful monitoring for efficacy of therapy. Somavert itself lacks intrinsic toxicity (if mistakenly dispensed to a non-acromegalic). Additionally, there are minimal to no consequences (in the short run) of undertreatment of acromegaly. Thus, the division maintains that the potential confusion with growth hormones and somatostatin analogue (Sandostatin-octreotide), another drug for the treatment of acromegaly, is unlikely to cause significant problems.

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/s/

David Orloff
3/25/03 11:53:28 AM
MEDICAL OFFICER

Office of Drug Safety

Memo

To: David Orloff, MD
Director, Division of Metabolic and Endocrine Drug Products
HFD-510

From: Denise P. Toyer, Pharm.D.
Team Leader, Division of Medication Errors and Technical Support
HFD-420

Through: Carol Holquist, RPh
Deputy Director, Division of Medication Errors and Technical Support
HFD-420

CC: Monika Johnson
Project Manager, Division of Metabolic and Endocrine Drug Products
HFD-510

Date: March 24, 2003

Re: ODS Consult 01-0008-01; Somavert (Pegvisomant for Injection); NDA 21-106

This memorandum is in response to the March 17, 2003 request from your Division for a re-review of the proprietary name, Somavert. We acknowledge the Division's decision to allow the sponsor to use the proprietary name Somavert despite DMETS' recommendation. We also note that container labels, carton and package insert labeling were not submitted for re-review.

In our original consult, dated March 21, 2001, DMETS did not recommend the use of the proprietary name Somavert. DMETS has not identified any additional sound-alike or look-alike names. However, DMETS has continuing concerns regarding the potential risk of medication errors with the use of the proprietary name Somavert. Our concerns as stated in the March 21, 2001 review are briefly summarized below:

- The primary concern is related to two look-alike drugs that already exist in the U.S. marketplace, namely Somatrem and Somatropin. An additional concern is the look-alike name, Somatostatin, which is not currently marketed in the U.S. However, the somatostatin analogue, Sandostatin (Octreotide) is available in the U.S. The manufacturer of Sandostatin indicated that practitioners often mistakenly prescribe

'Somatostatin' instead of 'Sandostatin.' Thus, DMETS must consider the potential name confusion between Somatostatin and Somavert. The product characteristics of Somavert, Somatrem, Somatropin, and Sandostatin are listed below.

	Somavert	Somatrem	Somatropin	Somatostatin
Established Name	Pegvisomant	Somatrem*	Somatropin	Octreotide
Proprietary Name	Somavert	Protropin	Genotropin Norditropin Nutropin Humatrope Serostim Saizen	Sandostatin (somatostatin** analogue)
Dosage Formulation	Lyophilized Powder	Lyophilized Powder	Lyophilized Powder	Solution for Injection
Dosage Strength	10 mg Vials 15 mg Vials 20 mg Vials	5 mg Vials 10 mg Vials	5 mg Vials 10 mg Vials	50 mcg/mL Ampule 100 mcg/mL Ampule 500 mcg/mL Ampule 200 mcg/mL 5 mL Vial 1000 mcg/mL 5 ml Vial
Route of Administration	Subcutaneously	Subcutaneously Intramuscularly	Subcutaneously Intravenously	Subcutaneously Intravenously
Frequency of Administration	Daily	Daily	Daily	BID, TID, or QID (depending upon indication)
Patient Population	Adults	Children	Children	Adults
Indication of Use	Acromegaly	Growth Hormone Deficiency	Growth Hormone Deficiency	Acromegaly Carcinoid Tumors Vasoactive Intestinal Peptide Tumors

* Product similarities are highlighted.
**Practitioners may write prescriptions for Somatostatin when they intend to prescribe Sandostatin. Sandostatin is available in the U.S.

- DMETS acknowledges that Somavert has Orphan Drug designation and that the population of patients being treated will be small. However, there is a potential for name confusion between Somavert and the existing somatostatin analogue within this small population. Additionally, the potential for name confusion between Somavert and Somatrem or Somatropin exists in healthcare facilities where both types of patients may be treated (e.g., large teaching facilities).

- DMETS agrees that healthcare practitioners exercise a level of scrutiny when administering injectable medications. However, medication errors associated with injectable medications occur despite the due diligence of healthcare practitioners. Examples of medication errors involving injectable medications include, but are not limited to, oral products being given intravenously, drugs administered via the wrong route of administration, and the administration of the wrong drug. The potential for these types of errors may increase when there are similarities in product names and/or packaging.

- DMETS' objective is to prevent medication errors from occurring. Thus, the occurrence of a medication error despite the outcome (nonserious or serious) would be concerning to DMETS.

- We note the Division's statement that growth hormone products are not distributed via pharmacies. However, we also note that prescriptions for growth hormones (e.g., Genotropin) may be filled via Internet pharmacies (i.e., http://www.destinationrx.com) or may be available in HMO, military, or hospital pharmacies.

- Container label, carton and package insert labeling comments were included in our initial review. Labels and labeling were not submitted for re-review.

Based on these concerns, DMETS does not recommend the use of the proprietary name Somavert.

If you have any questions or need clarification, please contact Sammie Beam at 301-827-3242.

APPEARS THIS WAY
ON ORIGINAL

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/s/

Denise Toyer
3/24/03 04:50:11 PM
PHARMACIST

Carol Holquist
3/24/03 04:52:23 PM
PHARMACIST

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration

Memorandum

Date: 5/15/01

From: Saul Malozowski
Medical Team Leader

Subject: Somavert, Pegvisomat, (NDA 21-106.) Name assignment.

To: David Orloff
Division Director, DMEDP

This memo is to reject DDMAC's recommendation to reconsider a name change for this product.

As with all medications there is always a risk for name confusion and/or a medical error when prescribing this product. Somavert, however, may pose fewer risks than other products because it is indicated only for a single and rare condition: acromegaly. As such the target population is very limited. This condition is even more rare in children, an it would be unlikely that will be sued in pediatric patients. In addition, being an injectable the level of scrutiny when administered will be higher than other products. Even if this product is mistakenly administered there are not known acute AE that may results from this action, except for those AE commonly associated to all injectables. To induce a negative pharmacological action this product will need to be administered chronically.

In summary, I do not think that the current name will pose undue risks or lead to medical errors if prescribed in error.

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/s/

Saul Malozowski
5/15/01 08:55:36 AM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research

DATE: March 6, 2003

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-106
Somavert (pegvisomant) injection
Pharmacia and Upjohn
Treatment of acromegaly

SUBJECT: NDA review issues and recommended action

Background

This application was AE'd on the first cycle principally because of multiple CMC deficiencies (described in the approvable letter of June 26, 2001). Notable among them was the low purity of the drug substance. A 6-month non-rodent toxicology study of daily administration of the to-be-marketed material was also required, as was a repeat rabbit teratology study. The sponsor submitted a complete response to the AE letter on September 27, 2002. In this and other correspondence the deficiencies were addressed. The rabbit teratology and non-rodent toxicity requirements were resolved since the purity of the to be marketed product is as high as the original product synthesized by [redacted] and previously studied in these toxicologic assays. The sponsor did conduct a 4-week bridging toxicology study comparing old [redacted] and new (to-be-marketed) product in rats that supported toxicologic identity. In addition, the eCAC has asked for a single phase IV carcinogenicity study. Pharmacia agreed to conduct a two-year carcinogenicity study in rats. In March 10, 2003, correspondence, the firm laid out the time for submitting the protocol, starting and completing the study, and submitting the final report.

Clinical

No new clinical efficacy data were reviewed on this cycle. Dr. Perlstein's review of the Safety Update covering the period from June 1, 2000, to July 18, 2002, revealed no new safety findings and raised no concerns. The additional exposure was minimal, however, limited to 25 more patients.

Labeling

Labeling has been negotiated between the sponsor and DMEDP. Input from Dr. Meyer (ODE 2) is pending. Information and recommendations on pre-treatment and on-treatment liver test monitoring are included.

There are no recommendations to follow GH levels or renal function. GH levels do appear to rise in patients treated with Somavert, though there are no clinical consequences apparent (and this does not appear to indicate growth of tumors during therapy). Standard of care (and the

label) hold that GH-secreting pituitary adenomas should be monitored periodically by imaging of the sella turcica.

The renal toxicity signal seen in animal toxicology studies has not been borne out in the clinical experience to date. No monitoring is recommended.

The sponsor does intend to create a database on clinical outcomes in patients treated with Somavert in an ongoing effort to understand the safety and efficacy of this novel therapy. Data will be collected on, among other things, renal and hepatic function. The division supports this activity.

Finally, the Division has discussed with the sponsor studies necessary to establish the therapeutic efficacy of a method of use that does not include a loading dose. We will work with the sponsor going forward on this issue.

Biopharmaceutics
No new biopharmaceutics data submitted.

Pharmacology/Toxicology
Approval, with a recommendation for a 2-year carcinogenicity study as a phase 4 commitment.

Chemistry/ Microbiology
Micro: AP recommendation.
CMC: The chemistry, manufacturing, and controls information is satisfactory and the application may be approved from the standpoint of ONDC. ONDC reviewer recommends 3 phase 4 commitments, as follows:

1. Develop an assay for use in release and stability testing of substance and product —— and implement a specification within one year of approval.
2. Validate the —— method currently used for testing of drug substance lots for the determination of the percentage of high molecular weight species and establish certain acceptance criteria based on this test.
3. Replacement of a statement from labeling of the diluent vial.

Pharmacia has agreed to the above (which we will call post-approval "agreements" because they don't involve "studies") in August 29, 2002, and March 7 and 10, 2003, submissions.

The establishment evaluations were all acceptable.
A categorical exclusion from the environmental assessment was claimed by the sponsor and accepted by the Agency.

DSI/Data Integrity
No issues currently.

Financial disclosure
No new issues.

ODS/nomenclature
DMETS recommended against the tradename during the first cycle. The division disagreed: orphan disease, daily injection, disease treated by specialists, monitoring for efficacy of therapy, lack of intrinsic toxicity of the drug, lack of consequences (in the short run) of undertreatment of acromegaly. Primary confusion was with somatostatin (Sandostatin—generic name for tradename error), another drug for the treatment of acromegaly.

DMETS was not reconsulted on the second cycle. No re-review is considered necessary. For the reasons above, medication errors are expected to be extremely unlikely, and if they do occur, of little consequence.

Recommendation
Approval.

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/s/

David Orloff
3/12/03 04:22:12 PM
MEDICAL OFFICER

MEMORANDUM

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

DATE: February 12, 2003

TO: David Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products
HFD-510

VIA: Monika Johnson, Pharm. D., Regulatory Health Project Manager,
Division of Metabolic and Endocrine Drug Products
HFD-510

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Anne Trontell, M.D., M.P.H., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: ODS/DSRCS Review of Patient Labeling for Somavert
(pegvisomant for injection), NDA 21-106

The patient labeling which follows represents the revised risk communication materials of the Patient Labeling for Somavert (pegvisomant for injection), NDA 21-106. We have simplified wording, made it consistent with the PI, removed promotional language per DDMAC recommendations (see DDMAC memo dated December 10, 2002) and other unnecessary information, and put it in the format that we are recommending for all patient information (a modified Medication Guide format). Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

Please let us know if you have any questions. Comments to the review Division are bolded, italicized, and underlined.

11 page(s) of revised draft labeling has been redacted from this portion of the review.

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/s/

Jeanine Best
2/12/03 02:38:54 PM
CSO

Toni Piazza Hepp
2/12/03 05:02:59 PM
PHARMACIST
for Anne Trontell

MEMORANDUM

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

DATE: January 31, 2003

TO: Division of Metabolic and Endocrine Drug Products, HFD-510

FROM: Monika Johnson, PharmD
Regulatory Review Officer

SUBJECT: **PASC and Wrap up Meeting**
NDA 21-106, Somavert (pegvisomant) for injection
January 21, 2002, Room 15B45

Attendees:

Dr. Robert Meyer, ODEII Director
Dr. David Orloff, DMEDP Division Director, Medical Team Leader
Dr. Robert Perlstein, Medical Reviewer
Dr. Hae-Young Ahn, Biopharmaceutics Team Leader
Dr. Xiaoxiong (Jim) Wei, Biopharmaceutics Reviewer
Dr. Eric Duffy, Division Director DNDCII
Janice Brown, MS, Chemistry Reviewer
Jenny Chang, PharmD, Safety Evaluator
Lahn Green, Safety Evaluator Team Leader
Sandra Birdsong, ODS PM
Dr. Lee Pian, Statistical Reviewer
Allen Brinker, Epidemiologist, ODS
Lee Ripper, ADRA ODEII
Monika Johnson, PharmD, PM

Dr. Perlstein gave an overview of the drug product, mechanism of action, and proposed indication, treatment of acromegaly. He outlined several safety issues that will be summarized in the PRECAUTIONS and ADVERSE REACTIONS sections of the package insert.

1. Growth Hormone elevation and potential tumor growth.
2. Immunogenicity and the clinical significance of antibodies to pegvisomant
3. Renal function testing
4. Functionally Growth Hormone deficient
5. Diabetics using Growth Hormone —glucose tolerance may increase
6. Liver Testing

Janice Brown gave an update on the pending chemistry issues. The diluent vial label contained the statement, [redacted] Will this statement be interpretative to the patient that the drug product should be administered intravenously.

Jim Wei had one comment about the Drug-Drug Interaction subsection on the package insert and that was that the statement, [redacted] that was deleted by the sponsor be returned to the package insert.

The members of the safety evaluation group had no comments or issues for the review team for pegvisomant.

APPEARS THIS WAY
ON ORIGINAL

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/s/

Monika Johnson
2/3/03 06:18:38 PM
CSO

Memorandum

Date: 6/25/01

From: Saul Malozowski
Medical Team Leader

Subject: Somavert, Pegvisomat, (NDA 21-106.) Team leader recommendations regarding the potential for renal compromise.

To: David Orloff
Division Director, DMEDP

This memo is to expand on my previous memo regarding the potential effects of Pegvisomat on the kidney. Preclinical data in rats suggest that this formulation could result in renal damage. No cases of renal insufficiency or progression of renal disease or proteinuria were seen in the limited patient population exposed. It is difficult to assess whether less important renal compromise was seen because no special considerations were given to this issue. In this regard, no creatinine clearances were requested and the little information on urinalyses performed at a central location render most of the information collected less than adequate. Information on urine sediments was sent for review several weeks ago and the MO was not able to render a definitive conclusion on this topic. There is no data to support renal compromise but it can not be definitively excluded either. This is a classical outcome in a safety review for a rare condition where few patients were exposed for a limited number of months.

The current label recommends urinalyses. It seems that this recommendation is the best we could do, at the present time, given the constraints imposed by the limited data and the quality of the tests performed.

Thus, I reiterate my previous recommendation to approve this application.

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/s/

Saul Malozowski
6/25/01 10:54:31 AM
MEDICAL OFFICER
This is to update the renal issues.

David Orloff
6/25/01 06:44:36 PM
MEDICAL OFFICER

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center For Drug Evaluation and Research

DATE: June 12, 2001

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-106
Somavert (pegvisomant) injection
Sensus Drug Development, Inc.

SUBJECT: NDA review issues and recommended action

Background

Pegvisomant is an analogue of human growth hormone that differs in 9 amino acid substitutions from the native molecule. As a result of these alterations, the molecule has a single functional binding site for the growth hormone receptor, but receptor dimerization, necessary for initiation of transmembrane signalling, does not ensue due to a non-functional second binding site. As such, pegvisomant is a growth hormone receptor antagonist with potential efficacy in the treatment of growth hormone excess. The peptide has been modified by covalent linking to polyethylene glycol (PEG) in order to delay clearance and increase the biological half-life of the drug. The drug has been studied in a series of clinical trials in acromegalics, [redacted] and normal volunteers, with a total of 160 acromegalics (84 treated for greater than one year) assessed for safety and efficacy and an additional approximately 80 non-acromegalic patients exposed and reported for the purposes of safety assessment in this NDA. The pegylated drug was originally intended for weekly administration, though the preliminary trials of this regimen failed to demonstrate satisfactory efficacy. The pivotal clinical information thus comes from trials of daily administration of pegvisomant.

Clinical

Safety

There were 2 deaths in the acromegaly trials in patients on pegvisomant, neither appearing related to drug. There were two reported serious adverse events attributed to pegvisomant by the medical reviewer. One involved a severe hypoglycemic episode and the other an unintentional overdosing of drug for one week of a six-month trial in which the patient administered 80 mg daily instead of 80 mg weekly. There were no apparent clinical consequences. There were very few adverse events leading to withdrawal, including one case of reversible lipohypertrophy at the injection site. Two patients discontinued due to 10 to 20-fold elevations in hepatic transaminase levels, one of whom underwent rechallenge in an extension study with recurrence of transaminase elevation, demonstrating a high likelihood of a drug effect. The other patient underwent liver biopsy with a final diagnosis of chronic hepatitis. The analysis of treatment emergent adverse events discussed on pages 74-76 of the medical review must, as Dr. Perlstein

points out, be interpreted with an understanding that the relatively few placebo patients contained in the safety database were treated for much shorter durations than were the pegvisomant patients. Specifically, the exposure to pegvisomant is approximately 20 times that to placebo. Needless to say, virtually all of the named adverse events are commonplace in acromegalics, thus the difference in incidence between pegvisomant and placebo may be legitimately attributed to differences in exposure.

Dr. Perlstein has appropriately reviewed the liver test data for all subjects enrolled in pegvisomant studies, not restricted to acromegaly, including those patients discontinued from pegvisomant but followed off therapy. With the caveat, as above, that the exposure to pegvisomant (193 patient-years) exceeds that to placebo or non-pegvisomant (60 patient-years) in this analysis, the overall difference in the rate of clinically significant transaminase elevations is not striking. With the exception of the two patients described above with isolated transaminase elevations, in one case attributed to pegvisomant, there were no elevations greater than 10 X ULN in either treatment group. Furthermore, in no case, including the case of presumed pegvisomant-induced transaminase elevation, was there a concurrent significant elevation in total bilirubin. The highest bilirubin among the patients with transaminase elevations $\geq$1.9X ULN was in a patient with a viral syndrome whose total bilirubin peaked at 1.4X ULN. Among the few patients with mild transaminase elevations at baseline, in no case was pegvisomant therapy associated with a further increase in ALT or AST. Indeed, in the majority of cases, levels normalized on therapy.

In light of the single case of apparent pegvisomant-induced transaminase elevation, Dr. Perlstein makes recommendations for baseline liver function testing and for follow up on therapy for two years and addresses work up and treatment of patients with baseline elevations. In addition, the sponsor has apparently stated a willingness to establish a registry of patients treated with the drug to better assess the risk and spectrum of liver toxicity, if it exists, of the drug.

The other safety issues raised by Dr. Perlstein include the following, with recommendations that they be addressed in labeling:

1. The potential for effective GH deficiency and the need to monitor IGF-1 levels.
2. The tendency for marked elevations in GH levels as a result of pegvisomant therapy (with no evidence of clinical consequence) though with a recommendation to follow levels.
3. The potential for growth of pituitary somatotroph adenomas possible related to pegvisomant therapy (i.e., in the absence of somatostatin analogue therapy that may directly inhibit growth).
4. The potential for increased insulin sensitivity due to blockade of GH-mediated counter-regulation.
5. The potential renal toxicity of pegvisomant due to the PEG component based on preclinical studies, though with no signal of renal effects in the clinical trials.

The antigenicity of pegvisomant has been investigated by assessment using an assay for anti-GH antibodies and using a specific assay for anti-pegvisomant antibodies of unknown validity. Suffice it to say that among the few patients with anti-GH or anti-pegvisomant antibodies, the titers were low, generally detectable only in sporadic samples, and not, apparently, of clinical

significance in affecting the efficacy of pegvisomant in lowering IGF-1. There were no cases of allergic reactions attributed to pegvisomant.

Efficacy

The pivotal trial, number 3614, enrolled 112 acromegalic patients, both male (56%) and female (44%), and randomized them to placebo, pegvisomant 10, 15, and 20 mg daily, in roughly equal numbers. Most patients had received previous therapy with surgery and/or radiation and/or drugs, and previous drug therapy was discontinued for the duration of the study. Patients were excluded if they had received long acting somatostatin analogue therapy in the preceding 3 months. Nine patients had received only drug therapy, and 4 patients were naïve to any therapy. The treatment groups were well matched for, among other variables, age, duration of disease, and mean IGF-1 level at baseline.

The primary analysis of efficacy was the mean percent change from baseline in serum IGF-1 concentration. The data are summarized in table 8 on page 51 of Dr. Perlstein's review. In brief, at the end of the 12-week study, the changes from baseline in IGF-1 for the placebo and pegvisomant 10, 15, and 20 mg daily dose groups, respectively, were –4%, -27%, -50%, and -63%. Substantial reductions from baseline in the pegvisomant groups were evident by week 2 of the trial and appear to plateau, on average, between weeks 4 and 8. Consistent with these dramatic reductions in mean IGF-1 levels, by the end of the study, 10%, 39%, 75%, and 82% of patients across the placebo and pegvisomant 10, 15, and 20 mg daily groups, respectively, achieved normalization of IGF-1 concentrations in serum. Dr. Perlstein presents an analysis on page 57 of his review that further suggests that larger (heavier) patients and those with higher baseline IGF-1 levels may require larger doses even than those studied to achieve optimal control of their disease as measured by normalization of IGF-1 concentrations.

These dose-dependent changes from baseline in IGF-1 were associated with salutary changes in a composite acromegaly symptom/sign score that included assessment of soft-tissue swelling, arthralgia, headache, excessive perspiration, and fatigue. The validity of the instrument utilized to assess these effects is not discussed, and it should be noted that these data represent non-primary endpoints of importance merely to confirm the primary biochemical endpoint analysis that establishes the effectiveness of pegvisomant in the treatment of acromegaly. Likewise, there were dose-related decreases in ring size in the pegvisomant treated groups relative to placebo, again confirming the primary endpoint outcome.

Among patients treated with somatostatin analogue therapy up to the randomization visit, treatment with pegvisomant resulted in an approximate doubling of the rate of normalization of IGF-1 levels from that visit to the end of the 12-week study, suggesting superior efficacy of the GH antagonist in this regard. Dr. Perlstein correctly points out that a prospectively designed trial is required to confirm this observation.

The overall efficacy of pegvisomant is confirmed in the other trials submitted to the NDA and reviewed in detail by Dr. Perlstein. These trials also demonstrated the durability of the effect of the drug out to one year of therapy. Specifically, during the one-year extension study, IGF-1 normalization was documented at 92% of patient visits, and in 71% of patients, IGF-1 was

normal at all visits. To the extent that morbidity, if not mortality, in acromegaly is presumed to depend on the integrated exposure to elevated IGF-1 levels, this analysis provides an important measure of the potential salutary effect of therapy in this disease on long-term sequelae of the condition.

Finally, the sponsor has proposed a 40-mg loading dose prior to initiation of daily pegvisomant therapy in acromegaly. The studies were conducted using a loading dose of 80 mg. The OCPB reviewer agrees that the PK data support the use of the smaller loading dose. Regardless, this is a drug intended for chronic use, and no acute therapeutic effect is necessary or expected. The time to steady state may be slightly longer with the lower dose, though this raises no clinical issues. The lower dose will necessitate a smaller volume injection and will, in theory, save on cost of treatment. If, indeed, there are any concerns over safety of this drug, the lower dose is prudent. Therefore, I concur with this recommendation.

Labeling
Revised labeling will be conveyed to the sponsor with the action letter.

Biopharmaceutics
The OCPB reviewer listed 4 comments for the sponsor that are conveyed in the action letter. These do not require resolution prior to approval. They are, briefly summarized, as follows:

1. Impurities in the drug product need to be identified and evaluated for cross-reactivity with pegvisomant in the pegvisomant-radioimmunoassay.
2. A drug interaction study with cyclosporine is recommended.
3. The route of elimination of pegvisomant needs to be elucidated.
4. In vitro metabolism/drug interaction studies are recommended as described in the CDER in vitro drug metabolism/drug interaction guidance.

As discussed under Clinical Efficacy, the OCPB reviewer addresses the issue of loading dose. Simulations submitted in the NDA of the effect on steady state PK of no loading dose or loading doses of 40, 60, or 80 mg suggest that after 6 weeks, the loading dose has no significance. Indeed, as discussed earlier, the disease is not one where immediate response is required and based on the pathophysiology of acromegaly, a rapid symptomatic response is hardly expected with this or any other form of treatment. Thus, it may be argued that a loading dose is not necessary and should either be eliminated or stated as optional. This may be resolved at a later date in discussion with the sponsor. In the meantime, as above, the 40 mg loading dose proposed by the sponsor is perfectly acceptable.

Pharmacology/Toxicology
The toxicology section of the NDA is insufficient to permit conclusions as to the spectrum of potential toxicity of the compound. The 6-month monkey study was invalid due to inadequate multiples of the human exposure at therapeutic doses. There were no major toxicities observed. The 6-month rat study did employ doses adequate to establish safety margins for the observed toxicities. At multiples of the human exposure, proteinuria and nephropathy were noted. The product studied was not mutagenic in standard assays or teratogenic in the rabbit.

Of note, the product used in all but the 6-month rat toxicology studies was 95% pure. The to-be-marketed product is only 55-75% pure. As a result, the pharmacologists have recommended further toxicology studies, including a 6-month non-rodent study and a rabbit teratology study. A two-year carcinogenicity study is required as a phase 4 commitment, and a phase 4 study to monitor renal function in patients treated with pegvisomant is also recommended. Assuming that the purity of the product is restored prior to approval, the non-rodent toxicology study will still be required, though the rabbit teratology study already conducted may suffice for approval.

Chemistry/ Microbiology

The chemistry, manufacturing, and controls information is not satisfactory, and the application is not approvable from the standpoint of ONDC. A large number of deficiencies were identified and are being conveyed in the action letter. CMC deficiencies relate to both drug substance and drug product and run the gamut from process, chemical characterization, specifications, and in-process controls. They are described in detail in the review and in the action letter.

As of May 30, 2001, the evaluation of the drug substance manufacturer ——— ——— was pending. The recommendation regarding the finished dosage release tester ——— ——— was "withhold." The report for the Drug Substance Other Tester was "OIA alert."

A categorical exclusion from the requirement to prepare an environmental assessment was requested and granted.

The microbiology reviewer was satisfied with the information provided on sterility assurance, with specific comments included in the action letter.

DSI/Data Integrity

Three clinical sites were audited. Two VAI and one NAI letter were issued for minor issues raised at inspection. DSI has concluded that the data from these sites are acceptable.

Financial disclosure

The financial disclosure information is in order and has been reviewed by Dr. Perlstein. He finds no reason for concern over data integrity as a result of the significant payments of other sorts reported in the NDA.

OPDRA

Safety consult

Dr. Senior has provided comment on Dr. Perlstein's recommendations with regard to hepatic monitoring and labeling. He concurs with the conservative approach recommended in light of the case of apparent pegvisomant-induced transaminase elevation and the relatively sparse exposure in pre-approval clinical trials.

Nomenclature

The OPDRA safety evaluator has recommended against the proprietary name, Somavert, due to the potential for confusion with somatrem, somatropin, and somatostatin. The first two are growth hormone products and the last is a product used for the treatment of esophageal varices

and enterocutaneous fistulas, though it is not marketed in the U.S. according the OPDRA reviewer.

Somatostatin analogues, such as Sandostatin, are used largely for the treatment of acromegaly, so there is no real danger of a substitution of Somavert for Sandostatin in acromegaly, should one occur. Pegvisomant appears to be a safe drug with no serious acute adverse effects (indeed no acute effects at all). Substitution of pegvisomant for growth hormone would therefore be unlikely to cause any acute problem. Substitution of growth hormone for pegvisomant would also be unlikely acutely to adversely affect an acromegalic. Finally, growth hormone products are not distributed through pharmacies in the U.S., but rather via direct distribution through other intermediaries to patients prescribed the products for labeled indications. As such, no pharmacist is able to make an error in filling a somavert prescription with a growth hormone product.

The current proposed name is acceptable.

Recommendation
This application is approvable pending addressing the multiple chemistry and pharm-tox deficiencies summarized above and conveyed in the action letter.

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/s/

David Orloff
6/13/01 07:46:48 PM
MEDICAL OFFICER

John Jenkins
6/20/01 02:42:03 PM
MEDICAL OFFICER
I concur with Dr. Orloff's recommendation that an AE letter be issued.

Memorandum

Date: 4/26/01

From: Saul Malozowski
Medical Team Leader

Subject: Somavert, Pegvisomat, (NDA 21-106.) Team leader recommendations.

To: David Orloff
Division Director, DMEDP

This memo is to support Dr. Perlstein's recommendations for this submission.

Somavert is a growth hormone (GH) receptor antagonist developed for the treatment of acromegaly. The studies performed indicate that Somavert is effective in significantly reducing biological markers of this condition. These changes are accompanied by regression of clinical signs and symptoms commonly seen in acromegalic patients. This compound provides a novel approach for the treatment of acromegaly and may result in beneficial effects in a large number of individuals where currently available therapies fail.

Because acromegaly is a rare condition, the number of patients exposed to Somavert was limited. The duration of treatment was also limited, as seen in many drug development plans for the treatment of other chronic conditions. Despite these evident limitations, the data collected indicates that Somavert is effective in reducing IGF-I levels. This reduction is rapid and sustained. Treated patients benefited to different extents from Somavert administration in controlling the underlying condition. The effect of the control was also durable. The primary end-point was defined as the percent change in IGF-I from baseline. The difference from placebo was 23, 44, and 58% change for the 10, 15 and 20 mg doses, respectively, after 12 weeks of therapy. All of these differences were statistically different from placebo. The percentage of patients normalizing IGF-I at endpoint, selected as a secondary endpoint, was 10, 39, 77 and 82% for the placebo, 10, 15 and 20 mg groups, respectively.

Several other variables were used as secondary endpoints. Among those, soft tissue swelling, arthralgia, headache, excessive perspiration, and fatigue were monitored. The 10 mg dose was more effective when compared to placebo only in the fatigue variable. The 15 and 20 mg doses were superior tp placebo in this variable and in soft tissue swelling and excessive perspiration. No differences between the placebo and any of the doses were seen in the headache and arthralgia variables. The ring size evaluation did not show any difference between placebo and the 10 mg dose. There was a significant difference between placebo and the 15 and 20 mg doses for this variable.

During the course of Somavert treatment, two patients (2/160-0.8%) had substantial elevations of liver enzymes (≥ 10X the upper limit of normal [ULN]). In one of them, a clear cause and effect relationship was demonstrated. The effects, however, were reversible. A liver consultant reviewed these data, and the medical reviewer has conveyed, at great length, the relevant information in his review and the label. Recommendations for monitoring for these potential hepatic complications are properly listed. It remains unclear whether this approach will reduce or avoid these potential complications. Because up to 30-40% treatment failures are seen with other anti-acromegalic therapies, the benefits from Somavert appear to overcome the risks associated with its use.

One not yet resolved issue relates to the significant incidence of low titers of anti-GH antibodies (~17%) observed while patients were receiving Somavert. This in turn may be, at least in part, associated with the lack of purity of this preparation since its production process was changed during the study rendering the product less pure. No treatment failures related to the presence of these antibodies, however, were observed. This suggests that the determination of anti-GH antibodies may be an adequate surrogate for anti-Somavert antibodies in assessing the impact of the immunogenicity of this product. Alternatively, the anti-GH antibodies determined may not be a good marker to assess immune response. I do not have the technical knowledge to properly address the quality of the determination of these antibodies, but the lack of clear treatment failures is reassuring.

Somavert was initially developed to be used as a long acting formulation. To accomplish this goal, the GH receptor antagonist was pegylated. In early development, it became apparent that weekly administration was ineffective and daily treatment was needed. This has presented several problems because the pre-clinical information does not cover for daily administration. Moreover, other pegylated products have been only approved for at the most every two-week administration. Preclinical data in rats suggest that this formulation could result in renal damage. No cases of renal insufficiency or progression of renal disease or proteinuria were seen in the limited patient population exposed. It is difficult to assess whether less important renal compromise was seen because no special considerations were given to this issue. In this regard, no creatinine clearances were requested and the little information on urinalyses performed at a central location render most of the information collected less than adequate. Information on urine sediments is forthcoming, but I am not hopeful that a definitive judgment can be rendered from these data. We also do not know whether there is a need to pegylate this protein; daily injections of the non-pegylated GH antagonist were not studied.

Tumor progression is commonly seen in acromegalic patients. The potential for tumor growth was considered early on during drug development because both the sponsor and the Division were concerned that a decrease in IGF-I might lead to increases in GH releasing hormone or decreases in somatostatin, which in turn could stimulate somatotrophs and subsequent tumor growth. The company analyses and the MO review indicate that tumor progression was only seen in two subjects (0.8%). In

addition, mean tumor volume was not increased during treatment. This information is very reassuring. Appropriate wording addressing this issue is included in the label.

Both the MO and the Biopharmaceutics team recommend a loading dose of 40 mg. This recommendation is based on information derived from a small number of patients (n~10) who by mistake received this dose instead of the 80 mg loading dose. In addition, PK/PD modeling further support initiating treatment with a 40 mg dose. Because most of the experience was accrued with the 80 mg dose, and this dose has been shown to be safe and effective, I will endorse this dose and not the 40 mg dose. The 40 mg dose could be included later in the label if a small study comparing these doses is conducted, and the 40 mg dose prospectively is shown to be equivalent to the 80 mg dose in controlling this condition.

Recommendations:

If the CMC and Pharmacology/Toxicology issues are properly resolved, and if appropriate changes currently under revision are made to the label, I will recommend the approval of this product.

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/s/

Saul Malozowski
5/2/01 02:49:05 PM
MEDICAL OFFICER
Team leader memo

David Orloff
5/24/01 04:51:45 PM
MEDICAL OFFICER

Meeting Minutes

IND	Trovert (pegvisomant) injection
Meeting Date:	October 7, 1999
Time:	10:00 am
Location:	Parklawn Conference Room 17B-43
Indication:	Acromegaly
Sponsor:	Sensus Drug Development Corp.
Type of Meeting:	CMC
Sponsor Contact:	Mike Bernstein @ 512-487-2018
Regulatory Project Manager:	Crystal King @ 301-827-6423
FDA Participants:	Stephen Moore, Ph.D., Chemistry Team Leader
	William Berlin, Ph.D., Chemistry Reviewer
	Crystal King, P.D., M.G.A., Regulatory Project Manager
Sponsor Participants:	William Bennett, Ph.D., Sr VP, Research, & Chief Scientific Officer
	Michael Bernstein, M.P.H., Senior Director, Regulatory Affairs
	Edward Calamai, Ph.D., Senior VP, Operations
	Eric Scharin, M.S., Manager, Manufacturing Services
	Nicholas Vrolijk, Ph.D., Director, Manufacturing Services
	David King, Ph.D., Representative, Pharmacia & Upjohn

Meeting Objective: To respond to the Division's request for technical information in support of an IND amendment filed 12/1/97 and to gain consensus on CMC issues prior to the NDA submission.

Background: A pre-NDA meeting was held on May 5, 1999. This meeting is to follow up on identified issues.

A meeting package was submitted to the IND on September 13, 1999.

After introductions, FDA presented responses to the questions presented by Sensus in overhead format. Additional significant points are summarized in *italics*.

Analytical Methods:

Stability:

Agenda Item 1: Does the Division concur that the stability data presented is adequate to support a label claim of 2-year shelf life for drug product stored at 25°C (*i.e.*, room temperature)?

Agency response:

- Acceptable. The Agency would like to discuss whether Tryptic Mapping would be a useful stability-indicating parameter.

  W. Berlin explained that some method is needed to demonstrate purity. S. Moore suggested that if the specification is not validated prior to the NDA submission, it could be a Phase 4 commitment due to the lateness of the request.

Validation:

Agenda Item 1: Does the Division agree with the scope, focus and timing of studies in-progress or planned for the purpose of validation of the analytical methods used to assess the quality, purity, identity, and safety of the drug substance and drug product?

Agency response:

These are all acceptable.

Agenda Item 2: Does the Division concur with the company that the scope of process validation studies now in progress or planned is adequate to support the validation of the bulk drug process?

Agency response:

These are adequate.

Agenda Item 3: Does the Division agree with the scope of studies planned or in-progress for validation of the pharmaceutical manufacturing of the final product (fill/finish)?

Agency response:

The scope of the studies is acceptable.

eNDA Submission:

Agenda Item 1: Is the company's plan to submit one executed manufacturing batch record each for both drug substance and drug product acceptable?

Agency response:

- Yes, this is acceptable.

  S. Moore indicated that a complete batch record is necessary.

Agenda Item 2: Is the company's plan to submit site specific information for only the drug product manufacturer, and not the drug substance manufacturer, in the eNDA appropriate?

Agency response:

- A floor diagram should be provided for both drug substance and drug product manufacturing facilities.

  S. Moore explained a blueprint was not necessary, only a demonstration.

Agenda Item 3: Does the Division concur with the planned manufacturing scale change in Q2-Q3, 2000?

Agency response:

- The full-scale commercial process should be submitted in the original NDA.
- The Agency recommends that the proposed scale-up change be implemented post-approval, rather than during the review clock.
- A comparability protocol may be discussed.

  W. Berlin indicated that the changes should be submitted as comparability studies to the NDA including the first three lots. The field inspectors will consider the implementation. E. Calamai indicated that Sensus will provide a summary and will be ready before and during the inspection windows.

Agenda Item 4: Does the Division concur with the timing for a PAI in conjunction with manufacturing runs scheduled for Q2-Q3, 2000?

Agency response:

- Acceptable – A reasonable PAI timing request may be included in the NDA cover letter.

  The Division can assist in encouraging the field, but we have no real control over this. With a priority review clock, an earlier inspection may be best.

Prepared by: *{see appended electronic signature page}*
Crystal King, P.D., M.G.A., Regulatory Project Manager

Concurrence: *{see appended electronic signature page}*
Stephen Moore, Ph.D., Meeting Facilitator

/s/

Stephen Moore
4/5/01 04:33:50 PM

Crystal King
4/5/01 10:27:21 AM

FDA CMC Meeting
October 7, 1999

Attendees:

Dr. Bill Berlin, Dr. Steve Moore, Crystal King (FDA)
Dr. Bill Bennett, Dr. Edward Calamai, Dr. Nick Vrolijk, Mike Bernstein, Eric Scharin (Sensus)
Dr. David King (Pharmacia-Upjohn)

Sensus requested the meeting for the purpose of discussing CMC-related topics, and posing specific questions related to development of B2036-PEG and preparation of the NDA submission.

A package of technical information and questions was sent to the Division in September for review before the meeting.

Analytical

Stability

1) The division agreed that the stability data presented was adequate to support a 2 year shelf life. They raised again the possibility of developing the tryptic map as a supportive method for assessing stability. Sensus presented data from recent oxidation studies (attached) where the tryptic map was able to detect changes to peptides containing methionine. FDA indicated that this would be another reason to try to incorporate tryptic mapping as a stability indicating method. Dr. Berlin raised the concern that peptide mapping is typically used as an identity test and may be difficult to validate theLimit of Detection (LOD) for use as a stability-indicating assay. Given Sensus' plans for filing of the NDA in the near future, FDA agreed to accept the attempted development and incorporation of this method as a phase IV (post-approval) commitment.

    - Sensus will implement develop work on the tryptic map as a stability indicating method (see comment under Analytical section).

Validation

1) FDA agreed with the scope, focus, and timing for validation of analytical methods
2) FDA agreed with the scope of the process validation studies planned.
3) FDA agreed with Sensus' plans for validation of the pharmaceutical process (fill / finish)

eNDA Submission

1) FDA agreed with the company's plans for submission of one (1) completed batch record for both the bulk and final product manufacturing. Dr. Moore recommended following the CBER/CDER Guidance (August '96) for the NDA format.
2) The Division requested a copy of the floor plan for both ——— Abbott.
3) Regarding proposed scale changes to the manufacturing process, FDA requested that any changes in process scale be delayed until after product approval. The

reason for this was that it might confuse the NDA review and pre-approval inspection if the batch records in the NDA were different than those being implemented during a PAI. Ed Calamai described the extent of scale changes planned and the rationale. Dr. Moore suggested a solution might be inclusion of a process comparability protocol in the NDA that referenced planned changes in the scale to be implemented during the next campaign (During 2000). This would be done in such a way as to allow field inspectors to be aware of pending changes, and review appropriate validation and testing prior to (or during) a PAI.

- Sensus will work with _____ to prepare a summary description of all proposed process changes, along with a Comparability Protocol to be executed during the commercial campaign.

4) The FDA agreed that the proposed timing seemed appropriate, however the timing is ultimately up to the field office. Additionally, since the NDA has fast track designation, this will help in the timing for the PAI. FDA asked whether _____ had been inspected by any local FDA offices, and indicated that it might be useful to arrange a meeting with the local office in advance of the formal PAI. In addition, a CMC reviewer from Washington and/or other biotech reviewers from the Boston or California offices might be involved with the PAI.

- Sensus and _____ will meet to discuss the value of contacting the district FDA office before the PAI is scheduled.

Other

Ed Calamai updated the Division on the development of a specific method for detection and quantitation of E. Coli Host Cell Proteins (HCP). A suitable antibody reagent has been identified, and Sensus expects that data from appropriate in-process testing would be included in the NDA filing. Full validation of the method would not be completed until post-filing.

Dr. Moore indicated that this was acceptable, but said that the method should eventually be validated to support process validation as well as lot release testing. Validation of the method should include verification of broad specificity for HCP, as well as LOD.

Release testing for HCP may be performed on the bulk intermediate or formulated bulk.

MEMORANDUM OF TELECON

DATE: July 12, 2001

APPLICATION NUMBER: NDA 21-106, Somavert (pegvisomant for injection)

BETWEEN:

Name: Robert Davis, Pharm.D., Executive Vice President, Sensus
Mark Mannebach, Associate Director Regulatory Affairs, Pharmacia
Clarice Haigh, CMC Regulatory Affairs, Pharmacia
Monica Johnson, Director of Toxicology, Pharmacia
James Moe, Vice President of Toxicology, Pharmacia

Representing: Sensus Drug Development Drug Corporation

AND

Name: Crystal King, P.D., M.G.A., Regulatory Project Manager
Jeri El-Hage, Ph.D., Pharmacology Supervisor
Fred Alavi, Ph.D., Pharmacology Reviewer
Division of Metabolic and Endocrine Drug Products, HFD-510

SUBJECT: Pharmacology/Toxicology Deficiencies

Following the Approvable Letter the Agency issued on June 26, 2001, the sponsor submitted a meeting request on July 2, 2001. The sponsor further referred to a discipline review letter issued on May 17, 2001, and responses submitted as an amendment on June 15, 2001. The June 26 deficiencies and requests, the May 17 review comments, the sponsor's questions, and the agreements reached are as follows.

Item 1:

Deficiency 17: A six-month non-rodent toxicology study with daily administration of the clinical formulation must be performed using drug product manufactured by the same facility and process as the to-be-marketed formulation. Since the drug product is covalently bonded to PEG, an additional control group with PEG-5000 (10 to 25 times human dose) is recommended.

Question: Based on the comprehensive information provided in the June 15 submission response to deficiency #1, Pharmacia/Sensus would like to know what additional safety information the FDA would expect to obtain as a result of conducting a repeat study in a non-rodent species?

Agreements: The toxicology data submitted in support of the NDA does not include a chronic toxicity study that adequately assesses the potential toxicity of Somavert. ICH S6 recommends six-month studies in two species be conducted to support the approval of biotechnology-derived products. While it was apparent at the time of

NDA filing that the monkey study was not adequately designed due to the weekly dosing regimen to support the safety of daily clinical use, the Division did file and complete a full review of the NDA since there had been a previous commitment to do so.

Upon full review of the NDA, it became apparent that in addition to the inadequacy of dosing frequency, the monkey studies were performed with the drug product manufactured by Genentech. The Genentech product was significantly more pure than the product manufactured by either of the P1 or P2 processes. Therefore, we do not have a non-rodent study which characterizes the toxicity of the to be marketed drug product.

In contrast to most drug products, the purity of the compound has deteriorated significantly over the course of development. Usually early toxicity testing with less pure product can be used to support the safety of clinical batches. However, when drug product purity declines over the course of development, the early studies with pure batches are not adequate to characterize toxicity of the impurities in later, less pure to-be-marketed drug product.

While the six-month rat study was conducted with the to-be-marketed drug product (P2 process) and daily drug administration comparable to the clinical dosing regimen, pegvisomant is not pharmacologically active in the rat. Therefore, this study does not provide information about potential target tissues in a pharmacologically responsive animal model.

In addition, in the six-month rat study carried out with the low purity P2 product, proteinuria and renal histopathology findings were observed. It is unclear whether these finding are attributable to PEG or other impurities. A study with daily dosing in monkeys with the to-be-marketed drug product (i.e., with acceptable purity) will also provide further information regarding whether renal toxicity is a concern with pegvisomant.

Dr. Haigh responded that it is Pharmacia's intent to make improvements in the manufacturing process to achieve product purity roughly comparable to that obtained with the original Genentech process (i.e., > 90% purity). In addition, Dr. Johnson stated that Pharmacia has pharmacokinetics data generated in conjunction with the six-month monkey study which demonstrate that drug exposures in monkeys dosed weekly exceed therapeutic exposures in patients dosed with 20 mg daily (C_{min} in monkeys dosed weekly > C_{ss} in subjects dosed daily, therefore, theoretically exposures over the dosing interval in monkeys should exceed clinical exposures). The Division responded that the additional monkey pharmacokinetics data, the chemistry comparability results, and the data demonstrating product purity comparable to the Genentech product should be provided for agency review. Based upon review of this data, the Division will determine whether the existing six-month monkey study can be deemed adequate.

Item 2:

Deficiency 18: Repeat the rabbit teratology study, and include at least one dose high enough to produce signs of maternal toxicity in rabbits using the to-be-marketed drug product.

Question: A rationale for dose selection was provided in the response to deficiency #2 in the June 15 submission. Based on the dose-finding study, we consider that the selected doses are justified. Is the FDA in agreement with our assessment? Considering that this compound should not be administered to pregnant women and that a study at high systemic exposure has been conducted, what further information would be derived by repeating the study with higher dosages?

Agreements: In the rabbit reproductive toxicity studies, the maximal dose evaluated of 10 mg/kg/day displayed minimal maternal toxicity. The dose range-finding study (conducted after the definitive studies) also utilized a maximal dose of 10 mg/kg/day. Since the decrements in body weight gain observed in the dose-finding study were not observed in the definitive reproductive toxicity studies, the dose-finding study is not adequate to demonstrate that 10 mg/kg/day was a maternal toxic dose.

The reproductive toxicity studies were conducted with the ——— P1 product (> 84% purity). If the manufacturing process is improved to achieve product purities greater than or equal to the P1 product, the Division would be willing to accept the completed reproductive toxicity studies since doses up to 10 times human exposures were utilized.

With changes in CMC, we can accept the completed studies.

Item 3:

Request 1: A two-year rodent carcinogenicity study should be conducted. Submit your plans for this study to include dates for submission of the final protocol, initiation of the study, completion of the study, and submission of the final report. We recommend you submit the protocol for review by our Executive Carcinogenicity Committee prior to initiation of the study. Additional carcinogenicity testing for this indication may not be needed pending a negative outcome of a valid study.

Question: Sensus previously submitted a request for a carcinogenicity study waiver along with a "white paper" to support this request in July of 2000. This supporting paper was also resubmitted in the June 15, 2001 response. Sensus never received a response from the FDA to this waiver request, nor have they had the opportunity to discuss with the FDA. Was the waiver request reviewed by the CAC, and, if so, what was the outcome?

Agreements: As early as July 1998, the division had communicated to the sponsor that in addition to short term *in vitro* and *in vivo* studies, at minimum a single carcinogenicity would be required for the acromegaly indication. For the acromegaly indication, the sponsor was permitted to perform the carcinogenicity study as a Phase 4 commitment. This requirement was imposed based on

discussions between Dr. Ronald Steigerwalt and Dr. Joseph DeGeorge, chair of the CAC, and still stands.

The negative *in vitro* and *in vivo* findings are supportive for the single Phase 4 carcinogenicity study position, but cannot replace a full carcinogenicity study.

The original recommendation from the Executive Carcinogenicity Assessment Committee (eCAC) was that two carcinogenicity studies should be completed prior to NDA filing. The Division compromised for the acromegaly indication to permit one study, post-approval. Therefore, it is not likely that eCAC would waive studies considering the original recommendation. Sensus has the option of resubmitting the white paper with its justification for waiving carcinogenicity studies for full review by the CAC.

Item 4:

Comment 4: A study monitoring renal function in acromegalic patients should be considered to assess the renal effects of chronic daily dosing of a pegylated compound.

Question: Pharmacia/Sensus response to deficiency #4 in the June 15 package addresses the safety/renal issues associated with PEG5000. Sensus has performed no specific studies of PEG5000. Published literature together with the results of the preclinical and clinical studies with pegvisomant have not demonstrated a safety profile of concern. There are also several other marketed products that utilize PEG5000 as a means to extend the circulating half-life (Oncaspar®, Adagen®, Pegylated Interferon). Is the FDA in agreement with our assessment?

Agreements: Although several other pegylated compounds are marketed, the dose, frequency, and duration of use for these drugs are significantly less than with Somavert. Therefore, previous clinical experience with these pegylated compounds does not assure the safety of Somavert. Whether PEG is the cause of the renal toxicity observed after chronic dosing in rats is not clear since the product used in rat study was the impure —— (P2) product. In addition, our review of the six-month monkey study revealed some minimal renal toxicity despite the less frequent dosing regimen.

Assessments of renal function in future clinical studies will provide definitive safety information to address concerns regarding the renal toxicity of Somavert arising from the preclinical findings.

See appended electronic signature page

Crystal King, P.D., M.G.A.
Regulatory Project Manager

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

/s/

Crystal King
8/2/01 04:22:26 PM

Tele-Con Meeting Minutes

IND# and Drug Name:	IND —— Trovert
Meeting Date:	May 5, 1999
Time:	3:00 pm
Indication:	Acromegaly
Sponsor:	Sensus
Type of Meeting:	Pre-NDA
Regulatory Project Manager:	Crystal King, P.D., M.G.A.
FDA Participants:	Solomon Sobel, M.D., Division Director
	Saul Malozowski, M.D., Ph.D., Medical Team Leader (Acting)
	Robert Perlstein, M.D., Medical Officer
	William Berlin, Ph.D., Chemistry Reviewer
	Todd Sahlroot, Ph.D., Biometrics Team Leader
	Ronald Steigerwalt, Ph.D., Pharmacology Team Leader
	Hae-Young Ahn, Ph.D., Biopharmaceutics Team Leader
	Robert Shore, Pharm.D., Biopharm Reviewer
Sponsor Participants:	John A Scarlett, M.D., CEO and President
	Robert Davis, Pharm.D, Executive Vice President
	Mike Bernstein, M.P.H., Senior Director, Regulatory Affairs
	Ed Calamai, Ph.D., Vice-President, Manufacturing
	Nick Vrolijik, Ph.D., Project Manager, Manufacturing & Controls
	——
	——
	Suzanne Hackett, M.S., Statistical Consultant
	——
	——

IND [redacted] May 5, 1999 Sensus

Background:

Trovert is a growth hormone antagonist being developed for the treatment of adults with acromegaly. The original IND was submitted on March 18, 1997; fast-track designation was granted March 18, 1999. Sensus wishes to secure Agency comment and confirmation of the planned NDA contents and data format in order to assure that the application may be filed and reviewed without significant delay or hindrance and will meet the Division's review needs.

DISCUSSION QUESTIONS:

Agenda Item 1: Does the Division agree on the studies to be included in the clinical and non-clinical sections of the electronic NDA (eNDA)?

A. Biopharm

- The presented studies are necessary, but not sufficient. Additional areas to be addressed:

  - absolute bioavailability (IV vs. SC)

  B. Davis indicated that SEN-3623 has been initiated.

  - metabolism and excretion; protein binding

  Action Item: [redacted] indicated that he could provide literature that concludes it is unlikely to get binding interference.

  - drug-drug interactions

  R. Perlstein indicated that we are interested in drugs which patients with acromegaly would likely be using. R. Shore stated that drug/drug interaction may or may not be a labeling issue. [redacted] noted that the population PK analysis would include concomitant medications by drug class.

  - multi-dose population PK--outline analysis protocol

  The protocol has been sent and appears fine to the Division.

  - markers (efficacy, toxicity) being used for PK/PD modeling

  B. Davis reported that IGF markers BP-3 and ALS are to be examined. Serum insulin declined.

  - bioequivalence, if clinical and commercial formulations differ

  The clinical and commercial formulations are the same.

  - PK in renal impairment

  [redacted] indicated that creatinine clearance would be checked in a population pharmacokinetic study and a bioavailability study. Then, it will be decided whether a renal impairment study is conducted or not. [redacted] noted that the distribution study in rats will measure activity and identify the excreted breakdown products. The rat kidney is more sensitive than the human kidney, so rats will show the maximum burden. The 3-month data for the 6-month rat study will be available later.

B. Pharm/Tox

- The proposed NDA package includes all the pharm/tox studies recommended to support an NDA for acromegaly. Some potential concerns include:

  - impact of the product on the kidney for renally-impaired patients

    ——— noted that there was no increase in BUN or creatinine clearance in humans after one year and nothing in animals.

  - the forms of product tested in the daily administration rat study compared to the clinical formulation (# of PEGs, etc.)

    N. Vorick stated that the manufacturing changes to the process are after the PEGylation. The product forms are identical.

  - the relative safety margin changes for patients with increased dosing

    ——— reported that this safety information would be included in the NDA. The rat study will be used to demonstrate toxicity. Patients will be monitored to insure no decrease in GH activity. The Division will take into account differences in animals and patients.

C. Pediatric:

-Please submit plans for pediatric drug development studies, waiver, or deferral.

M. Bernstein indicated that Sensus plans to request a waiver, as the product is not intended for pediatric use.

Agenda Item 2: Does the Division agree on the groupings and presentation of the ISS?

*Yes.

Agenda Item 3: Does the Division agree on the groupings and presentation of the ISE?

*Yes.

Agenda Item 4: Does the Division agree on the format and datasets for the eNDA?

*Additionally, we need:

- all biopharm raw data on diskette

Sensus will follow the January, 1999 CDER guidance.

- Pop PK and PD control streams

—— will provide the NONMEM data.

- derived SAS datasets for efficacy and safety, by individual patient (detail will be discussed before data submission)

M. Bernstein indicated that individual patient profiles would be in the dataset and have hyperlinks; this was acceptable.

—— questioned if the CRF tab data sets need every field or just key parameters. T. Sahlroot indicated that only the key parameters are necessary. Sensus should use "best judgment" as to critical listings.

Action Item: —— will send a listing and proposal for the Division statistician to review.

The Division indicated that our preference is for one record per patient instead of a stacked file. Results may be given without parameters.

Agenda Item 5: Does the Division require any portion of the eNDA to be in paper?

* We would like:

- eight desk copies of the first two volumes (including index, labeling, ISS, and ISE)
- one copy of Section 6 (human PK) of everything except the data sets (data sets to be provided on diskettes as above)
- one copy of chemistry batch records
- one copy of Section 10 (statistics)

Sensus will follow the January 1999 Guidance document in providing the specified review copies.

Agenda Item 6: Additional Comments

*T. Sahlroot conferred with —— J. Scarlett, R. Davis, and M. Bernstein regarding the statistical analysis plan for study SEN-3614.

- The sponsor had proposed a repeated measures analysis at weeks 8 and 12. FDA recommended that each time point be examined separately, with the 12-week results considered as primary.
- Regarding the proposed multiple-comparison, step-down procedure, the Division noted the risk with this approach which starts by comparing the high dose to placebo at the 0.05 level. If the

result is not statistically significant, the medium and low doses would not be tested. This procedure compares to a Dunnett's procedure which allows a comparison of each dose with placebo with statistical adjustment for multiple comparisons.

Sensus will discuss this and will send an amendment if changes are adopted. The sponsor does not anticipate marketing the product if the 20mg dose doesn't work.

/S/

Prepared by: 6/4/99

Crystal King, R.D., M.G.A., Regulatory Project Manager

Meeting Chair: /S/ 6/4/99

Saul Malozowski, M.D., Ph.D., Medical Team Leader (Acting)

Concurrence:	Solomon Sobel, M.D., Division Director	ncr by	6/04/99
	Robert Perlstein, M.D., Medical Officer	ncr by	6/04/99
	William Berlin, Ph.D., Chemistry Reviewer	ncr by	6/04/99
	Todd Sahlroot, Ph.D., Biometrics Team Leader		5/28/99
	Ronald Steigerwalt, Ph.D., Pharmacology Team Leader		6/01/99
	Hae-Young Ahn, Ph.D., Biopharmaceutics Team Leader		6/04/99
	Robert Shore, Pharm.D., Biopharmaceutics Reviewer		6/04/99

Attachments: A) Sensus pre-meeting package of March 23, 1999
B) Sensus letter of April 28, 1999
C) Sensus meeting minutes for May 5, 1999

cc: IND —— (with attachments)
HFD-510 Division File (without attachments)
HFD-510: CKing, SSobel, SMalozowski, RPerlstein, WBerlin, RSteigerwalt, HAhn, RShore, TSahlroot (without attachments)

ATTACHMENT B

sensus

28 April 1999

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Rockville, MD 20857

Dear Crystal:

I am writing on behalf of Mike Bernstein in order to provide the attached overview of the PEGylation of Growth Hormone Antagonist (GHA). We have prepared this overview in advance of our pre-NDA teleconference next week in an attempt to clarify any questions regarding the quality and uniformity of the PEGylated GHA used in both non-clinical and clinical studies, or the reproducibility of our manufacturing process. Please forward this overview to Bill Berlin at your earliest convenience and we look forward to discussing this issue on Wednesday (5 May).

Best regards,

Nick Vrolijk

Nick Vrolijk, Ph.D.
Project Manager

Enclosure
cc: M. Bernstein, J. Scarlett, E. Calamai, B. Bennett, B. Davis

4 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.