

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**APPROVAL PACKAGE FOR:**

**APPLICATION NUMBER**

**21-106**

**Chemistry Review(s)**

NDA 21-106  
SOMAVERT (pegvisomant for injection) 10, 15, 20 mg

CHEMISTRY DIVISION DIRECTOR REVIEW

**Applicant:** Pharmacia & Upjohn

**Indication:** Treatment of acromegaly

**Presentations:** Lyophilized powder in single-dose sterile glass vials packaged with a plastic vial with 10 mL of Sterile Water for Injection

**EER Status:** acceptable, 11/26/2002

**Consults:** OPDRA , acceptable 5/15/2001; Microbiology, acceptable 11/25/2002; EA, acceptable 1/16/2003

Somavert (pegvisomant for injection) is a product of pegylated human growth hormone (hGH) antagonist produced by recombinant DNA technology for treatment of acromegaly. The protein portion of this molecule contains nine amino acid changes from native human growth hormone. These changes collectively enable it to block binding of native growth hormone thereby preventing receptor dimerization and serves as a growth hormone receptor antagonist. The applicant indicates that an optimum of 4 – 5 covalently linked PEG 5000 to the protein prolongs the in vivo half-life of the molecule.

Somavert is available in single-dose, sterile glass vials in three strengths, 10mg, 15mg, and 20 mg (protein only) co-packaged with 10 mL of Sterile Water for Injection, USP for reconstitution. The drug substance is manufactured by \_\_\_\_\_

Abbott Laboratories at

McPherson, KS manufacture the drug product for Pharmacia & Upjohn while the diluent, WFI, USP, is manufactured by Abbott Laboratories, at Rocky Mount, NC.

Somavert was originally developed by Sensus Drug Development Corporation at Austin, Texas before the ownership of Sensus was transferred to Pharmacia in 2001. An NDA submitted by Sensus in December 22, 2000 was not approved due to significant deficiencies. To address the CMC deficiencies delineated in the AE letter dated 6/26/01, Pharmacia has resubmitted the complete NDA to describe all the changes which include 1) recharacterization of the reference standard, 2) addition of new manufacturers and a new method of manufacture, 3) revised process controls, 4) production of new reference standards, 5) revised specifications for the drug substance and drug product, and 6) submitted new stability data for the drug substance and drug product. There have been three changes in the manufacturing processes related to purity for pegvisomant drug substance since the contract manufacturer was switched from Genetech to \_\_\_\_\_

3.

The shelf-life of the drug substance is 12-months when stored at  $-70^{\circ}\text{C}$  in \_\_\_\_\_ bottles. The shelf-life of the drug product is 18-months when stored at  $2-8^{\circ}\text{C}$ . The reconstituted drug product is to be used within 6 hours at  $15-25^{\circ}\text{C}$  when stored in vials or polypropylene syringes. All were supported by stability data

**Overall Conclusion:**

From a CMC perspective the application is recommended for approval.

Duu-Gong Wu, PhD  
Deputy Director, DNDC II/ONDC

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this page is the manifestation of the electronic signature.

/s/

Duu-gong Wu  
3/24/03 12:57:22 PM  
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2.24.03  
AP**NDA #21-106****SOMAVERT™****Pharmacia & Upjohn****Janice Brown, HFD-510  
Division of Metabolic and Endocrine Drug  
Products**

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# Chemistry Review Data Sheet

1. NDA: 21-106
2. REVIEW #: 3
3. REVIEW DATE: 19-Feb-2003
4. REVIEWER: Janice T. Brown/ONDC/DNDC2 (HFD-510)
5. PREVIOUS DOCUMENTS:

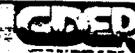
<u>Previous Documents</u>	<u>Document Date</u>	<u>Previous Documents</u>	<u>Document Date</u>
N-000	22-Dec-2000	N-000	21-May-2002
N-000	22-Feb-2001	N-000	27-Sep-2002
N-000	17-Apr-2001	N-000	09-Oct-2002
N-000C	17-Apr-2001	N-000	04-Nov-2002
N-000BC	18-Apr-2001		
N-000BC	18-Apr-2001		
N-000	23-Apr-2001		
N-000BL	24-Apr-2001		
N-000	25-Apr-2001		
N-000	01-May-2001		
N-000	29-May-2001		
N-000	04-Jun-2001		
N-000	25-Jun-2001		
N-000	05-Nov-2001		

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed:</u>	<u>Document Date</u>
N000BC	31-May-2002
N000BZ	29-Aug-2002
N000BC	09-Oct-2002
N000BC	04-Nov-2002
N000BC	26-Nov-2002
N000BC	10-Feb-2003
N000BL	13-Feb-2003



# CHEMISTRY REVIEW



Chemistry Review Data Sheet

## 7. NAME & ADDRESS OF APPLICANT:

Name: Pharmacia & Upjohn  
Address: 7000 Portage Road  
Kalamazoo, MI 49001-0199  
Representative: Satish C. Tripathi, Ph.D., Director, Global  
Regulatory Affairs  
Telephone: (616) 833-4000

## 8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: SOMAVERT
- b) Non-Proprietary Name (USAN): (Pegvisomant for injection)
- c) Code Name/# (ONDC only): N/A
- d) Chem. Type/Submission Priority (ONDC only):
  - Chem. Type: Type 1 (NME)
  - Submission Priority: Priority

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: GH receptor antagonist

11. DOSAGE FORM: Lyophilized Powder for Injection

12. STRENGTH/POTENCY: 10mg, 15mg, and 20mg (as protein)

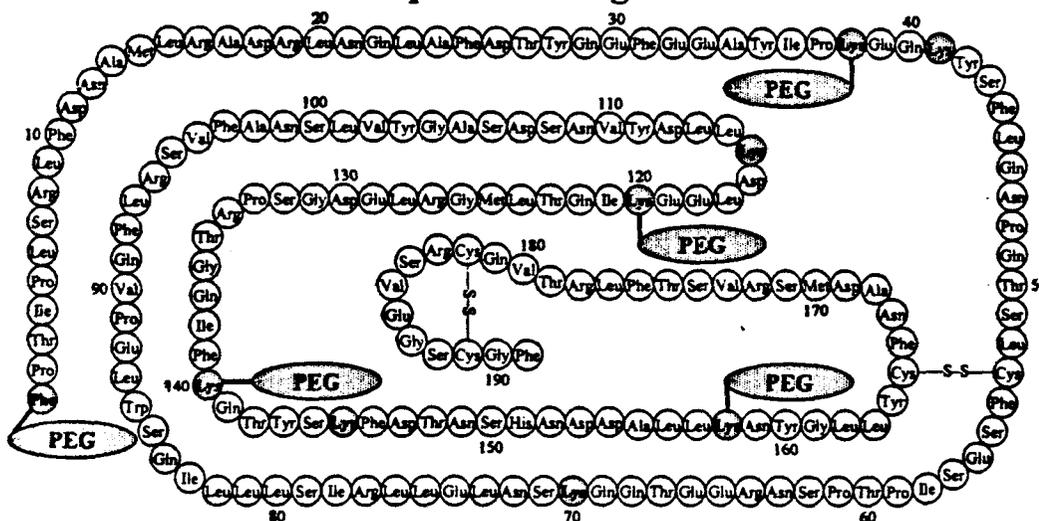
13. ROUTE OF ADMINISTRATION: Subcutaneous

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note27]:

SPOTS product – Form Completed

Not a SPOTS product

**16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA; MOLECULAR WEIGHT:**
**Amino Acid Sequence of Pegvisomant Protein**


\* Stippled residues indicate PEG attachment sites (Phe<sub>1</sub>, Lys<sub>38</sub>, Lys<sub>41</sub>, Lys<sub>70</sub>, Lys<sub>115</sub>, Lys<sub>120</sub>, Lys<sub>140</sub>, Lys<sub>145</sub>, Lys<sub>152</sub>)

**Chemical Name:**

Proprietary: Somavert™ (Pegvisomant for injection)

Established: Pegvisomant (B2036-PEG)

Company or laboratory code:

Drug Product: B2036-PEG

Drug Substance: B2036-PEG, Growth Hormone Antagonist (GHA)

Intermediate: B2036 (before pegylation)

Chemical Name: 18-L-aspartic acid-21-L-lysine-167-L-asparagine-168-L-alanine-171-L-serine-172-L-arginine-174-L-serine-179-L-threonine growth hormone (human), reaction product with polyethylene glycol growth hormone antagonist.

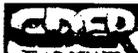
Molecular Formula: C<sub>980</sub>H<sub>1519</sub>N<sub>259</sub>O<sub>303</sub>S<sub>7</sub> - [(CH<sub>2</sub>CH<sub>2</sub>O)<sub>112 ± 10%</sub> - CH<sub>2</sub>CH<sub>2</sub>O]<sub>4-5</sub>

Molecular Weight: The predominate molecular weights are 42, 47, and 52 kDa.

**17. RELATED/SUPPORTING DOCUMENTS:**

**A. DMFs: See review #1**

**B. Other Documents: See review #1**



# CHEMISTRY REVIEW



## Chemistry Review Data Sheet

### 18. STATUS:

### ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	NA		
EES	Acceptable	26-Nov-2002	S. Ferguson (HFD-324)
Pharm/Tox	Acceptable	02-Dec-2002	F. Alavi (HFD-510)
Biopharm	NA	NA	NA
LNC	See OPDRA review	NA	NA
Methods Validation	In process		
OPDRA	Not Acceptable; overridden by Medical - Team Leader Medical Team Leader	04-Apr-2001  15-May-2001	Hye-Joo Kim (HFD-420)  S. Malozowski (HFD-510)
EA	Acceptable	16-Jan-2003	J. Brown (HFD-510)
Microbiology	Acceptable	25-Nov-2002	J. McVey (HFD)

The application submission(s) covered by this review was taken in the date order of receipt.

Yes  No If no, explain reason(s) below:

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this page is the manifestation of the electronic signature.**

/s/

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Janice Brown  
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Stephen Moore  
2/24/03 02:49:36 PM  
CHEMIST



# CHEMISTRY REVIEW



## Attachment 8: OC recommendation for the manufacturing sites

19-DEC-2002

FDA CDER EES

Page 1 of 3

### ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Application: NDA 21106/000	Priority: 1F	Org Code: 510
Stamp: 26-DEC-2000 Regulatory Due: 31-MAR-2003	Action Goal:	District Goal: 27-APR-2001
Applicant: PHARMACIA AND UPJOHN	Brand Name: SOMAVERT (PEGVISOMANT)	
7000 PORTAGE RD	Established Name:	
KALAMAZOO, MI 49001	Generic Name: PEGVISOMANT	
	Dosage Form: FLJ (FOR INJECTION)	
	Strength: 5.0, 7.5, 10.0 MG/ML	
<hr/>		
FDA Contacts: C. KING (HFD-333)	301-827-7317	Project Manager
J. BROWN (HFD-510)	301-827-6421	Review Chemist
S. MOORE (HFD-510)	301-827-6430	Team Leader

Overall Recommendation:

ACCEPTABLE on 26-NOV-2002 by S. FERGUSON (HFD-324) 301-827-0062  
 WITHHOLD on 26-JUN-2001 by E. HARTMAN (HFD-324) 301-827-0067

Establishment: 1921343	DMF No:	
ABBOTT LABORATORIES	AADA No:	
HWY 301 NORTH 4285 NORTH WEST		
ROCKY MOUNT, NC 27804		
<hr/>		
Profile: WSP	OAI Status: NONE	Responsibilities: FINISHED DOSAGE STERILIZER
Last Milestone: OC RECOMMENDATION		
Milestone Date: 24-SEP-2002		
Decision: ACCEPTABLE		
Reason: BASED ON FILE REVIEW		

Establishment: 1925262	DMF No:	
ABBOTT LABORATORIES	AADA No:	
1776 NORTH CENTENNIAL DR		
MCPHERSON, KS 67460		
<hr/>		
Profile: SVL	OAI Status: NONE	Responsibilities: FINISHED DOSAGE MANUFACTURER
Last Milestone: OC RECOMMENDATION		
Milestone Date: 07-OCT-2002		
Decision: ACCEPTABLE		
Reason: DISTRICT RECOMMENDATION		

Establishment:	DMF No:	
	AADA No:	
<hr/>		
Profile: CTL	OAI Status: NONE	Responsibilities:
Last Milestone: OC RECOMMENDATION		
Milestone Date: 26-NOV-2002		

Continued



# CHEMISTRY REVIEW



19-DEC-2002

FDA CDER EES

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## ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Decision: **ACCEPTABLE**  
Reason: **DISTRICT RECOMMENDATION**

Establishment: \_\_\_\_\_ DMF No:  
AADA No:

Profile: **CBI** OAI Status: **NONE** Responsibilities: \_\_\_\_\_  
Last Milestone: **OC RECOMMENDATION**  
Milestone Date: **18-NOV-2002**  
Decision: **ACCEPTABLE**  
Reason: **DISTRICT RECOMMENDATION**

Establishment: \_\_\_\_\_ DMF No:  
AADA No:

Profile: **CTL** OAI Status: **NONE** Responsibilities: \_\_\_\_\_  
Last Milestone: **OC RECOMMENDATION**  
Milestone Date: **02-OCT-2002**  
Decision: **ACCEPTABLE**  
Reason: **DISTRICT RECOMMENDATION**

Establishment: \_\_\_\_\_ DMF No:  
AADA No:

Profile: **CTL** OAI Status: **NONE** Responsibilities: \_\_\_\_\_  
Last Milestone: **DO RECOMMENDATION**  
Milestone Date: **18-DEC-2002**  
Decision: **ACCEPTABLE**  
Reason: **DUPLICATE MILESTONE FROM FA**

Establishment: **1810109** DMF No:  
**PHARMACIA CORP** AADA No:  
**7000 PORTAGE RD**  
**KALAMAZOO, MI 49001**

Profile: **SVL** OAI Status: **NONE** Responsibilities: **FINISHED DOSAGE LABELER**



# CHEMISTRY REVIEW



19-DEC-2002

FDA CDER EES

Page 3 of 3

## ESTABLISHMENT EVALUATION REQUEST SUMMARY REPORT

Last Milestone: **OC RECOMMENDATION**  
Milestone Date: **03-OCT-2002**  
Decision: **ACCEPTABLE**  
Reason: **DISTRICT RECOMMENDATION**

---

**DIVISION OF METABOLIC AND ENDOCRINE DRUG PRODUCTS**  
**Review of Chemistry, Manufacturing, and Controls**

**NDA #:** 21-106

**DATE REVIEWED:** 22-Jun-01

**REVIEW #:** Chemistry review #2

**REVIEWER:** Janice Brown, HFD-510

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	22-Dec-00	26-Dec-00	02-Jan-01
Correspondence	17-Apr-01	18-Apr-01	
Amendment	18-Apr-01	19-Apr-01	
Amendment	23-Apr-01	24-Apr-01	
Amendment	25-Apr-01	26-Apr-01	
Amendment	01-May-01	02-May-01	
Amendment	29-May-01	30-May-01	
Amendment	04-Jun-01	05-Jun-01	

**NAME & ADDRESS OF APPLICANT:** Sensus Drug Development Corporation  
98 San Jacinto Blvd.  
Suite 430  
Austin, Texas 78701

**DRUG PRODUCT NAME**

**Proprietary:** Somavert®

**Established:** Pegvisomant for injection

**Code Name/#:** B2036-PEG

**Chem.Type/Ther.Class:** Type 1P, Growth Hormone Antagonist (GHA)

**PHARMACOL. CATEGORY/INDICATION:**

**DOSAGE FORM:** Powder for injection

**STRENGTHS:** 10, 15, and 20 mg vial

**ROUTE OF ADMINISTRATION:** Subcutaneous injection.

**Rx/OTC:**  Rx  OTC

**SPECIAL PRODUCTS:**  Yes  No

( If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

CHEMICAL NAME-STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

**Structural Formula:** The bold and underlined positions are sites at which significant polyethylene glycol attachment (>20%) has been observed.

1 E P T I P L S R L F D N A M L R A D R L  
21 N Q L A F D T Y Q E F E E A Y I P K E Q  
41 K Y S F L Q N P Q T S L C F S E S I P T  
61 P S N R E E T Q Q K S N L E L L R I S L  
81 L L I Q S W L E P V Q F L R S V F A N S  
101 L V Y G A S D S N V Y D L L K D L E E K  
121 I Q T L M G R L E D G S P R T G Q I F K  
141 Q T Y S K F D T N S H N D D A L L K N Y  
161 G L L Y C F N A D M S R V S T F L R T V  
181 Q C R S V E G S C G F

Disulfide bonds: Cys<sub>53</sub>-Cys<sub>165</sub>  
Cys<sub>182</sub>-Cys<sub>189</sub>

Chemical Name: Pegvisomant for injection  
Molecular Formula: C<sub>980</sub>H<sub>1519</sub>N<sub>259</sub>O<sub>303</sub>S<sub>7</sub> • [(CH<sub>2</sub>CH<sub>2</sub>O)<sub>112</sub> ± 10% - CH<sub>2</sub>CH<sub>2</sub>O]<sub>4-5</sub>  
Molecular Weight: 42,000 - 47,000 Daltons

SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date	Letter Date
DMF			Acceptable	20-Dec-00	NA
DMF			NA	NA	NA
NDA 18-801 (HFD-170)	Sterile Water for Injection USP	Abbott Labs	Approved 27-Oct-1982	NA	NA

\*Inactive DMF, extractable and cytotoxicity results are reviewed in the Drug Product section under the subheading Container/Closure.

RELATED DOCUMENTS (if applicable): None

CONSULTS:

Microbiology Review  
OPDRA Labeling Review

REMARKS: Review #2 is written in response to a tertiary review on Chemistry review #1 performed by Dr. Yuan-yuan Chiu, ONDC management, revised labeling submission, and for an update of the GMP status of the manufacturing facilities.

CONCLUSIONS & RECOMMENDATIONS:

The Chemistry, Manufacturing and Controls (CMC) information provided in this application is not satisfactory. This application is NOT APPROVABLE from a CMC standpoint.

The previous EER summary report included two sites where a recommendation was pending. An updated EER summary report indicated that \_\_\_\_\_ facilities had a "Withhold" recommendation (see Establishment Inspection Section). Satisfactory inspections of all listed facilities are required before this application may be approved.

**/S/**

\_\_\_\_\_  
Janice Brown, Review Chemist

NA

cc: Org. NDA 21-106  
HFD-510/Division File  
HFD-510/J. Brown/3-5-01  
HFD-510/S. Moore  
HFD-820/Y.Y. Chiu, C. Hoiberg (NMEs only)  
R/D Init by: S. Moore, Teamleader

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FDA CDER EES  
ESTABLISHMENT EVALUATION REQUEST  
SUMMARY REPORT

**INADEQUATE SPECIFICATIONS**

Establishment: \_\_\_\_\_ DMF No:  
\_\_\_\_\_ AADA No:

Profile: CTL OAI Status: NONE Responsibilities: \_\_\_\_\_  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 03-APR-2001  
Decision: ACCEPTABLE  
Reason: DISTRICT RECOMMENDATION  
FIRM RESPONSE TO DEFIC. ADEQ

Establishment: 1810189 DMF No:  
PHARMACIA AND UPJOHN CO AADA No:  
7000 PORTAGE ROAD  
KALAMAZOO, MI 49001

Profile: SVL OAI Status: NONE Responsibilities: FINISHED DOSAGE LABELER  
Last Milestone: OC RECOMMENDATION  
Milestone Date: 01-FEB-2001  
Decision: ACCEPTABLE  
Reason: BASED ON PROFILE

Establishment: \_\_\_\_\_ DMF No:  
\_\_\_\_\_ AADA No:

Profile: CTL OAI Status: OAI ALERT Responsibilities: \_\_\_\_\_  
Last Milestone: DO RECOMMENDATION  
Milestone Date: 19-JUN-2001  
Decision: WITHHOLD  
Reason: INADEQUATE LAB CONTROLS  
PREVIOUS DEVIATIONS PERSIST

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/s/

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Janice Brown  
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Stephen Moore  
6/25/01 12:57:37 PM  
CHEMIST

DIVISION OF METABOLIC AND ENDOCRINE DRUG PRODUCTS  
Review of Chemistry, Manufacturing, and Controls

NDA #: 21-106

DATE REVIEWED: 10-Mar-01

REVIEW #: Chemistry review #1

REVIEWER: Janice Brown, HFD-510

<u>SUBMISSION TYPE</u>	<u>DOCUMENT DATE</u>	<u>CDER DATE</u>	<u>ASSIGNED DATE</u>
ORIGINAL	26-Dec-00	26-Dec-00	02-Jan-01
Correspondence	17-Apr-01	18-Apr-01	
Amendment	18-Apr-01	19-Apr-01	
Amendment	24-Apr-01	25-Apr-01	
Amendment	25-Apr-01	26-Apr-01	
Amendment	01-May-01	02-May-01	

NAME & ADDRESS OF APPLICANT: Sensus Drug Development Corporation  
98 San Jacinto Blvd.  
Suite 430  
Austin, Texas 78701

DRUG PRODUCT NAME

Proprietary: Somavert™ (Pegvisomant for injection)

Established: Pegvisomant

Code Name/#: B2036-PEG, Growth Hormone Antagonist (GHA)

Chem.Type/Ther.Class: Type 2

PHARMACOL. CATEGORY/INDICATION:

DOSAGE FORM: Powder for injection

STRENGTHS: 10, 15, and 20 mg vial

ROUTE OF ADMINISTRATION: Subcutaneous injection.

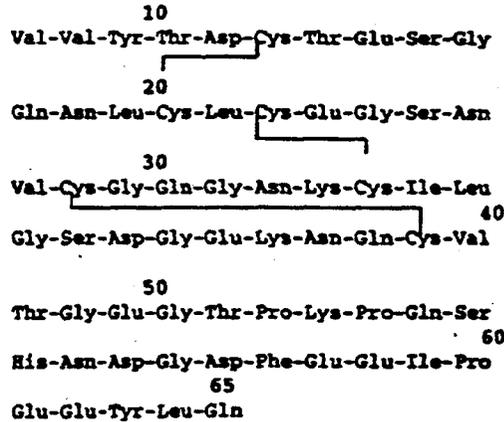
Rx/OTC:  Rx  OTC

SPECIAL PRODUCTS:  Yes  No

( If yes, fill out the form for special products and deliver to TIA through team leader for data entry)

**CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:**

Structural Formula:



Chemical Name: desirudin, CGP 39393, or RPR 205511  
Molecular Formula:  $C_{287}H_{440}N_{80}O_{110}S_6$   
Molecular Weight: — Daltons

**SUPPORTING DOCUMENTS:**

Type/Number	Subject	Holder	Status	Review Date	Letter Date
DMF	_____		Acceptable	20-Dec-00	NA
DMF	_____		NA	NA	NA

\*Inactive DMF, extractable and cytotoxicity results are reviewed in the Drug Product section under the subheading Container/Closure.

**RELATED DOCUMENTS (if applicable):** None

**CONSULTS:** None

**REMARKS:** See Summary.

**CONCLUSIONS & RECOMMENDATIONS:**

The Chemistry, Manufacturing and Control (CMC) information provided in this application is not satisfactory. This application is NOT APPROVABLE from a CMC standpoint.

An Establishment Evaluation Request (EER) was requested on 31-Jan-01 for the listed sites and includes the following recommendations.

Name of Manufacturer/Tester

Recommendation  
Pending

Pharmacia and UpJohn  
Abbott Laboratories

Acceptable  
Pending (OAI Alert)  
Acceptable  
Acceptable

/S/

Janice Brown, Review Chemist

cc: Org. NDA 21-106  
HFD-510/Division File  
HFD-510/J. Brown/3-5-01  
HFD-510/S. Moore  
HFD-820/S. Koepke, C. Hoiberg (NMEs only)  
R/D Init by: S. Moore, Teamleader

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/s/

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Janice Brown  
5/31/01 11:12:08 AM  
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Stephen Moore  
5/31/01 01:50:40 PM  
CHEMIST



-----  
Establishment : CFN : 1925262 FEI : 1925262

ABBOTT LABORATORIES  
1776 NORTH CENTENNIAL DR  
MCPHERSON, KS 67460

DMF No:

AADA:

Responsibilities: FINISHED DOSAGE MANUFACTURER

Profile : SVL OAI Status: NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 07-OCT-02

Decision : ACCEPTABLE

Reason : DISTRICT RECOMMENDATION

-----  
Establishment : EI : 1000121235  
