CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-271

CHEMISTRY REVIEW(S)

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

NDA #: 21-271 **DATE REVIEWED:** 10-Mar-01

REVIEW #: Chemistry review #1 **REVIEWER:** Janice Brown, HFD-510

SUBMISSION TYPE	DOCUMENT DATE	CDER DATE	ASSIGNED DATE
ORIGINAL	28-Jun-2000	28-Jun-2000	05-Feb-01

NAME & ADDRESS OF APPLICANT: Aventis Pharmaceuticals Products, Inc.
500 Arcola Road
P.O. Box 1200
Collegeville, PA 19428-0107

DRUG PRODUCT NAME

Proprietary: —

Established: USAN/WHO name: Desirudin

Code Name/#: CGP 39393, Ciba-Geigy AG control number
RPR 205511, Rhone-Poulenc Rorer control number

Chem.Type/Ther.Class: Type 2

PHARMACOL. CATEGORY/INDICATION: For the prevention of deep vein thrombosis, which may lead to pulmonary embolism/in patients undergoing elective hip replacement surgery for the prevention of deep vein thrombosis/which may lead to pulmonary embolism/in patients undergoing elective hip replacement surgery

DOSAGE FORM: Lyophilized powder for injection

STRENGTHS: 15 mg

ROUTE OF ADMINISTRATION: Subcutaneous injection.

Rx/OTC: _X_ Rx ___ OTC

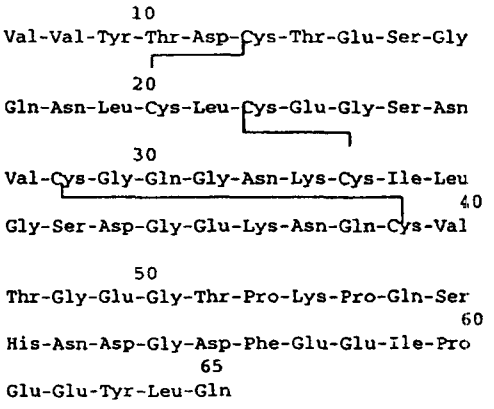
SPECIAL PRODUCTS: _X_ Yes ___ No

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

APPEARS THIS WAY
ON ORIGINAL

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: 6963.52 Daltons

SUPPORTING DOCUMENTS:

Type/Number	Subject	Holder	Status	Review Date	Letter Date
DMF [redacted]	[redacted]	[redacted]	Acceptable	6-23-99	NA

RELATED DOCUMENTS (if applicable): None

CONSULTS: This is a consult review for the Division of Gastrointestinal and Coagulation Drug Products (HFD-180) for recombinant hirudin variant 1, also called desirudin. This CMC review is for the drug substance only.

REMARKS: Desirudin differs from natural hirudin by the absence of a O-SO_3H at Tyr63. This product is a potent thrombin inhibitor and will be used to prevention of deep vein thrombosis. The issues identified in this review include the addition of in-process controls in the [redacted] steps and drug substance specification limits.

CONCLUSIONS & RECOMMENDATIONS: The issues identified in this review should be forwarded to the sponsor either as an information request or in an approvable letter.

The following methods should be forwarded to FDA laboratories:
[redacted] to determine potency.
HPLC to determine content

Janice Brown, Review Chemist

APPEARS THIS WAY
ON ORIGINAL

cc: Org. NDA 21-271
HFD-510/Consult 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

/s/

Janice Brown
3/26/01 11:22:51 AM
CHEMIST

Stephen Moore
3/26/01 03:22:31 PM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL

(1)

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

65

CMC Review 1st Review Cycle

DIVISION OF GASTROINTESTINAL AND COAGULATION DRUG PRODUCTS
Review of Chemistry, Manufacturing and Controls

NDA: 21-271 **Chem. Review: #1** **Review Date: 4/9/01**

Submission Type	Document Date	CDER Date	Assigned Date
BZ	March 27, 2001	March 28, 2001	
BZ	March 19, 2001	March 20, 2001	March 22, 2001
BC	March 5, 2001	March 6, 2001	
BZ	March 2, 2001	March 5, 2001	March 13, 2001
BL	March 2, 2001	March 5, 2001	March 13, 2001
BZ	December 19, 2000	December 20, 2000	December 20, 2000
BZ	October 11, 2000	October 12, 2000	
Original	June 28, 2000	June 28, 2000	July 27, 1998

Name and Address of Applicant:
Aventis Pharmaceuticals
500 Arcola Road
Collegeville, PA 19426

Drug Product Name:
Proprietary: [redacted]
Non-proprietary/USAN: Desirudin
Code Number (laboratory): CGP39393
Trivial Names: recombinant Hirudin, rHirudin, rDesulfato Hirudin r[Tyr63]-hirudin sequence variant 1
Chem. Type/Ther. Class: 2S/anticoagulant

ANDA Suitability Petition/DESI/Patent Status: A request for three-year patent exclusivity is made under 21CFR314.108(b)(5). Patent # 4,745,177 and 4,801,576 cover the drug substance, formulation, composition, and method of use of [redacted]

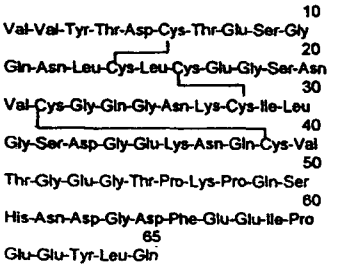
Pharmacological Category /Indications:
-selective thrombin inhibitor
[redacted]

Dosage Form: lyophilized powder for reconstitution
Strength: 15 mg per vial
Route of Administration: subcutaneous injection

How Dispensed: ___√___ R_x _____OTC

Special Product: ____ No √ Yes

Chemical Name, Molecular Formula, Molecular Weight, Structural Formula
Chemical Name : r[Tyr^{63}]-hirudin sequence variant 1
Structure:



Molecular Formula: $C_{287}H_{440}N_{80}O_{110}S_6$
Molecular Weight: 6,963.52 daltons

Related Documents: None
Supporting Documents: None

Consults:

Drug substance. Review. Review completed; resolution of deficiencies pending.
Biopharm. Review. Review completed; resolution of deficiencies pending.
Sterility Review: Review completed; resolution of deficiencies pending.
Toxicology Review. Review pending.
OPDRA Review: — was judged to be an unacceptable name for this product.

Remarks/Comments

The drug substance is manufactured using recombinant DNA technology. To improve product stability, the proposed commercial formulation has been significantly changed from the formulation used in clinical trials. The major issues requiring resolution are: 1) an explanation why the biological activity, as determined by the fibrin clot assay, is consistently — higher in the commercial batches than in the clinical batches, 2) satisfactory justification of the 5% vial overfill of the lyophilized product, 3) assurance that the required label dose can be accurately delivered with the recommended administration instructions, 4) setting appropriate specifications for individual and total known and unknown impurities and related substances, and 5) resolution of the issues cited in the consulting reviews.

Conclusions and Recommendations

From the CMC perspective, this NDA is considered approvable pending resolution of the issues cited in the deficiency letter.

Marie Kowblansky, PhD
Review Chemist, HFD-180

Liang Zhou, PhD
Chemistry Team Leader, HFD-180

cc: Orig. NDA 21-271
HFD-180/Division File
HFD-180/LTalarico
HFD-180/CSO/BStrongin
HFD-820/Directors
HFD-180/LZhou
HFD-180/MKowblansky

(E)

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

(18)

Application: **NDA 21271/000** Priority: **S** Org Code: **180**
Stamp: **28-JUN-2000** Regulatory Due: **14-MAY-2001** Action Goal: District Goal: **15-MAR-2001**
Applicant: **AVENTIS PHARMS** Brand Name: [redacted] **(DESIRUDIN) 15MG**
C/O QUINTILES INC Established Name:
9708 Generic Name: **DESIRUDIN**
KANSAS CITY, MO 641340708 Dosage Form: **INJ (INJECTION)**
Strength: **15 MG**

FDA Contacts: **M. KOWBLANSKY (HFD-180)** **301-827-7310 , Review Chemist**
L. ZHOU (HFD-150) **301-594-5765 , Team Leader**

Overall Recommendation:

ACCEPTABLE on 12-JAN-2001 by M. GARCIA (HFD-322) 301-594-0095

Establishment: [redacted] DMF No:
[redacted] AADA No:
[redacted]

Profile: **SVL** OAI Status: **NONE** Responsibilities: [redacted]
Last Milestone: **OC RECOMMENDATION**
Milestone Date **24-AUG-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: [redacted] DMF No:
[redacted] AADA No:
[redacted]
[redacted]

Profile: **SVL** OAI Status: **NONE** Responsibilities: [redacted]
Last Milestone: **OC RECOMMENDATION**
Milestone Date **05-SEP-2000**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

Establishment: **9692036** DMF No:
NOVARTIS PHARMA INC (CIBA) AADA No:

CH-4002, BASEL, , SZ

Profile: **CFN** OAI Status: **NONE** Responsibilities: **DRUG SUBSTANCE MANUFACTURER**
Last Milestone: **OC RECOMMENDATION**
Milestone Date **12-JAN-2001**
Decision: **ACCEPTABLE**
Reason: **DISTRICT RECOMMENDATION**

/s/

Marie Kowblansky
4/11/01 03:12:17 PM
CHEMIST

Liang Zhou
4/11/01 04:16:05 PM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL

CHEMISTRY REVIEW

NDA #21-271

IPRIVASK

Aventis Pharmaceuticals

Janice Brown, HFD-180
Division of Gastrointestinal and Coagulation Drug Products

Table of Contents

Chemistry Review Data Sheet

1. NDA: 21-271

2. REVIEW #: 2

3. REVIEW DATE: 24-Feb-2003

4. REVIEWER: Janice T. Brown/ONDC/DNDC2 (HFD-510)

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Original	28-Jun-2000

6. SUBMISSION(S) BEING REVIEWED:: Drug Substance Section Only

Submission(s) Reviewed	Document Date
N-000AZ	03-Oct-2002
N-000BC	21-Feb-2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Aventis Pharmaceuticals Products, Inc
Address:	500 Arcola Road
Representative:	P.O. Box 1200
Telephone:	Collegeville, PA 19428-0107

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: Iprivask™ (desirudin) Injection
b) Non-Proprietary Name (USAN): Desirudin for Injection
Code Name/# (ONDC only): CGP 39393, Ciba-Geigy AG control number
RPR 205511, Rhone-Poulenc Rorer control number
c) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: Type 2
- Submission Priority:

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

10. PHARMACOL. CATEGORY: For the prevention of deep vein thrombosis, which may lead to pulmonary embolism/in patients undergoing elective hip replacement surgery for the prevention of deep vein thrombosis/which may lead to pulmonary embolism/in patients undergoing elective hip replacement surgery

11. DOSAGE FORM: Lyophilized powder for injection

12. STRENGTH/POTENCY: 15 mg

13. ROUTE OF ADMINISTRATION: Subcutaneous injection

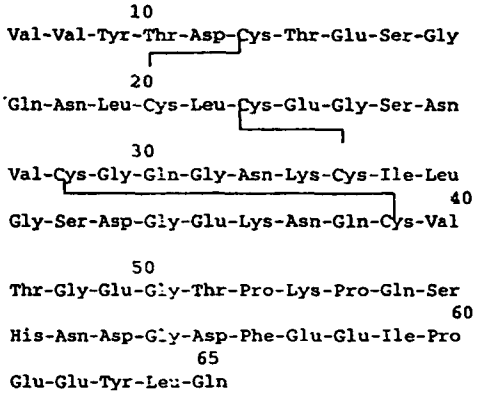
14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note26]:
___X__SPOTS product – Form Completed

_____Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Structural Formula:



Chemical Name: r[Tyr63]-Hirudin sequence variant 1
desirudin, CGP 39393, or RPR 205511
Molecular Formula: $C_{287}H_{440}N_{80}O_{110}S_6$
Molecular Weight: 6963.52 Daltons

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
DMF	3	—	[ ]	1	Acceptable	6-23-99	None

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

APPEARS THIS WAY ON ORIGINAL

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18. STATUS: See Dr. Kowblansky's CMC review

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
CMC (Drug Substance)	Acceptable	27-Feb-2003	J. Brown, HFD-510
Biometrics			
EES			
Pharm/Tox			
Biopharm			
LNC			
Methods Validation			
OPDRA			
EA			
Microbiology			

OGD:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology			
EES			
Methods Validation			
Labeling			
Bioequivalence			
EA			
Radiopharmaceutical			

19. ORDER OF REVIEW (OGD Only)

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for NDA 21-271

Consultative Review for Drug Substance

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From a chemistry standpoint the drug substance section of this NDA is acceptable. See Drug Product review for overall CMC approvability status.

The following should be communicated to the applicant:

1. **A shelf life of 24-months for the drug substance stored at [redacted] is granted instead of a retest period.**
2. **The firm should be notified that a method identifier (e.g., alphanumeric code number) should be included on the drug substance specification sheet.**

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance - Desirudin is a recombinant protein produced in *Saccharomyces cerevisiae* strain [redacted], transformed with [redacted]. It has a protein structure that is similar to that of hirudin, the naturally occurring anticoagulant present in the peripharyngeal glands in the medicinal leech, *Hirudo medicinalis*. Desirudin is a single polypeptide chain of 65 amino acids residues and contains three disulfide bridges. It has a chemical formula of $C_{287}H_{440}N_{80}O_{110}S_6$ with a molecular weight of 6963.52. Desirudin differs from the natural hirudin by lack of a sulfate group on Tyr-63. The biological activity of desirudin is determined through a chromogenic assay that measures the ability of desirudin to inhibit the hydrolysis of a chromogenic peptide substrate by thrombin in comparison to a desirudin standard.

Drug Product – Refer to Dr. Kowblansky's CMC review.

B. Description of How the Drug Product is Intended to be Used

See Dr. Kowblansky's CMC review.

C. Basis for Approvability or Not-Approval Recommendation

The applicant has addressed all the outstanding CMC deficiencies for the Drug Substance as listed in the Agency's AE letter dated 14-May-2001 and the teleconference on 24-Jan-2003

III. Administrative

A. Reviewer's Signature - see appended electronic signature page.

B. Endorsement Block

Janice Brown (HFD-510)/25-Feb-2003
Stephen Moore (HFD-510)/25-Feb-2003
Alice Kacuba (HFD-180)/25-Feb-2003

C. CC Block: HFD-180/Division File

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

/s/

Janice Brown
2/27/03 02:49:10 PM
CHEMIST

Stephen Moore
2/27/03 03:20:01 PM
CHEMIST

APPEARS THIS WAY
ON ORIGINAL

(F)

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

NDA 21-271

Iprivask™
(desirudin)

Aventis Pharmaceuticals Inc.

Marie Kowblansky, Ph.D.
DIVISION OF GASTROINTESTINAL AND COAGULATION
DRUG PRODUCTS

Table of Contents

CHEMISTRY REVIEW

Chemistry Review Data Sheet

1. NDA 21-271

2. REVIEW #2

3. REVIEW DATE: December 20, 2002

4. REVIEWER: Marie Kowblansky, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
BZ	March 19, 2001
BC	March 5, 2001
BZ	March 2, 2001
BL	March 2, 2001
BZ	December 19, 2000
BZ	October 11, 2000
Original	June 28, 2000

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
BZ	October 14, 2002

7. NAME & ADDRESS OF APPLICANT:

Name:	Aventis Pharmaceuticals
Address:	500 Arcola Road Collegeville, PA 19426
Representative:	Tracey Atherton, R.Ph. Quintiles, Inc. Kansas City, MO
Telephone:	816-767-6000

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: IPRIVASK™
b) Non-Proprietary Name (USAN): Desirudin
c) Code Name/# (ONDC only): CGP39393, recombinant Hirudin, rHirudin, rDesulfato Hirudin
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 2
- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:
(A request for three-year patent exclusivity is made under 21CFR314.108(b)(5). Patent # 4,745,177 and 4,801,576 cover the drug substance, formulation, composition, and method of use of IPRIVASK)

10. PHARMACOL. CATEGORY:
-selective thrombin inhibitor

11. DOSAGE FORM:
-lyophilized powder for injection

12. STRENGTH/POTENCY: 15 mg per vial

13. ROUTE OF ADMINISTRATION: subcutaneous injection

14. Rx/OTC DISPENSED: _√__Rx ___OTC

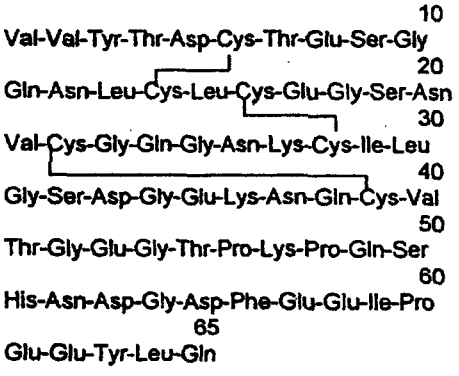
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note26]:

___√___SPOTS product – Form Completed
_____Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name : r[Tyr^{63}]-hirudin sequence variant 1

Structure:



Molecular Formula: $C_{287}H_{440}N_{80}O_{110}S_6$

Molecular Weight: 6,963.52 daltons

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	3	[redacted]	[redacted]	4	NA		----

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
– Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
----	----	----

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not required		
EES	Acceptable	October 23, 2002	
Pharm/Tox	pending		
Biopharm	pending		
Drug substance	pending		J. Brown HFD-180
LNC	Acceptable	April 16, 2001	D. Boring. His comments have been incorporated into the review of the original submission under "Labeling"
Methods Validation	pending		
OPDRA	pending		
EA	Categorical exclusion	April 16, 2001	M. Kowblansky (see review of original submission)
Microbiology	pending		

The Chemistry Review for NDA 21-271

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry perspective, this application is considered Approvable pending resolution of the following issues:

1) In the original submission, the biological activity of the drug product, as determined by the fibrin clot assay, was consistently — higher in the commercial batches than in the clinical batches, although both products were formulated to contain the same amount of drug substance. Since this would result in a superpotent product, compared to the clinical trial batches, the applicant was requested to provide an explanation of the bioassay results. However, the response provided in the current submission is not adequate, lacking data to support the applicant's conclusion that the biological activity is actually the same, just different standards were used in the assay of clinical and commercial batches. Additional information has been requested in an IR letter dated December 5, 2002.
2) Administration of the recommended dose requires the removal of the entire (0.5 mL) reconstituted solution from the vial. In the reviewer's opinion this can result in significant dose variability, i.e. subpotent dosing. USP recommends that each vial be filled with a volume in slight excess of the volume that is to be withdrawn. The final decision on the acceptability of the proposed dosing approach in a hospital setting will be be made in conjunction with the medical reviewer and the Office of Drug Safety.
3) Satisfactory resolution of additional issues cited in the Draft Deficiency Letter

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable – None at this time.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The active drug substance in IPRIVASK is desirudin, a protein having the same amino acid sequence and structure as natural hirudin (sequence variant 1), but lacking the sulfate group at tyrosine 63. It is produced by recombinant DNA technology from yeast cells.

The drug product will be marketed as a single dose (15 mg) freeze-dried powder with an accompanying sterile non-pyrogenic reconstitution solvent (3% aqueous mannitol in Water for Injection). The product is manufactured to contain a 5% overfill of the lyophilized drug product in the vial, i.e. 15.75 mg desirudin. Administration instructions call for reconstitution of the lyophilized drug product with 0.5 mL of the 3% mannitol solution, followed by withdrawing the entire contents of the vial for administration to the patient. The 5% overfill of the lyophilized drug product in the vial compensates for the small amount of solution that remains behind in the vial and allows for withdrawal of the required 15 mg of desirudin on administration.

B. Description of How the Drug Product is Intended to be Used

The recommended dose is 15 mg, administered subcutaneously twice daily for nine to twelve days.

C. Basis for Approvability or Not-Approval Recommendation

Pending resolution of the issues itemized under section II.A., above, the application is approvable since the drug product will meet the required quality standards that will make it as safe and effective as the drug tested in clinical trials.

III. Administrative

A. Reviewer's Signature

Marie Kowblansky, PhD
Review Chemist, HFD-180

Liang Zhou, PhD
Chemistry Team Leader, HFD-180

B. Endorsement Block

ChemistName/Date: Marie Kowblansky 12/20/02
ChemistryTeamLeaderName/Date Liang Zhou.
ProjectManagerName/Date Alice Kacuba

(G)

THIS SECTION WAS DETERMINED NOT TO BE RELEASABLE

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

/s/

Marie Kowblansky
12/20/02 11:14:17 AM
CHEMIST

Ali AlHakim is Acting team leader for Liang Zhou

Ali Al-Hakim
12/23/02 02:02:03 PM
CHEMIST

APPEARS THIS WAY ON ORIGINAL

NDA 21-271

Iprivask™
(desirudin)

Aventis Pharmaceuticals Inc.

Marie Kowblansky, Ph.D.
DIVISION OF GASTROINTESTINAL AND COAGULATION
DRUG PRODUCTS

Table of Contents

CHEMISTRY REVIEW

Chemistry Review Data Sheet

1. NDA 21-271

2. REVIEW #3

3. REVIEW DATE: February 15, 2003

4. REVIEWER: Marie Kowblansky, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
BZ	October 14, 2002
BZ	March 19, 2001
BC	March 5, 2001
BZ	March 2, 2001
BL	March 2, 2001
BZ	December 19, 2000
BZ	October 11, 2000
Original	June 28, 2000

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
BC	January 7, 2003
BC	January 24, 2003
BC	February 20, 2003
BC	February 21, 2003

7. NAME & ADDRESS OF APPLICANT:

Name:	Aventis Pharmaceuticals
Address:	500 Arcola Road Collegeville, PA 19426
Representative:	Tracey Atherton, R.Ph. Quintiles, Inc. Kansas City, MO
Telephone:	816-767-6000

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: IPRIVASK ™
b) Non-Proprietary Name (USAN): Desirudin
c) Code Name/# (ONDC only): CGP39393, recombinant Hirudin, rHirudin, rDesulfato Hirudin
d) Chem. Type/Submission Priority (ONDC only):

- Chem. Type: 2

- Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION:
(A request for three-year patent exclusivity is made under 21CFR314.108(b)(5). Patent # 4,745,177 and 4,801,576 cover the drug substance, formulation, composition, and method of use of IPRIVASK)

10. PHARMACOL. CATEGORY:
-selective thrombin inhibitor

11. DOSAGE FORM:
-lyophilized powder for injection

12. STRENGTH/POTENCY: 15 mg per vial
(formulated to contain 15.75 mg/vial; following administration instructions results in delivery of 15 mg dose.)

13. ROUTE OF ADMINISTRATION: subcutaneous injection

14. Rx/OTC DISPENSED: √ Rx ___OTC

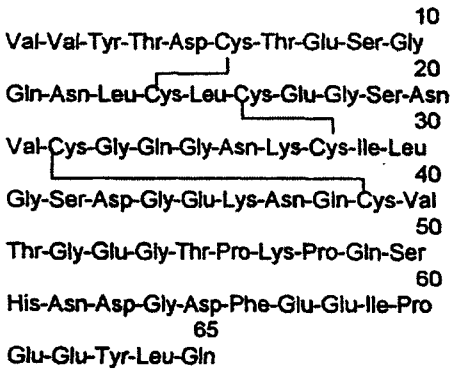
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM)[Note26]:

___√___SPOTS product – Form Completed
_____Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemical Name : r[Tyr^{63}]-hirudin sequence variant 1

Structure:



Molecular Formula: $C_{287}H_{440}N_{80}O_{110}S_6$

Molecular Weight: 6,963.52 daltons

APPEARS THIS WAY
ON ORIGINAL

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF =	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
[redacted]	3	[redacted]		4	NA		----

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate. Inadequate. or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
----	----	----

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	Not required		
EES	Acceptable	October 23, 2002	See appended report
Pharm Tox	Approval	February 28, 2003	
Biopharm	Approval	February 12, 2003	
Drug substance	Approval	February 27, 2003	J. Brown HFD-180
LNC	Acceptable	April 16, 2001	D. Boring. His comments have been incorporated into the review of the original submission under "Labeling"
Methods Validation	pending		
OPDRA	Acceptable	December 5, 2002	Jerry Phillips
EA	Categorical exclusion	April 16, 2001	M. Kowblansky (see review of original submission)
Microbiology	Approval	March 3, 2003	P. Stinavage

APPEARS THIS WAY
ON ORIGINAL

The Chemistry Review for NDA 21-271

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the CMC perspective, this application may be approved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable – None at this time.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

The active drug substance in IPRIVASK is desirudin, a protein having the same amino acid sequence and structure as natural hirudin (sequence variant 1), but lacking the sulfate group at tyrosine 63. It is produced by recombinant DNA technology from yeast cells.

The drug product will be marketed as a single dose (15 mg) freeze-dried powder with an accompanying sterile non-pyrogenic reconstitution solvent (3% mannitol in Water for Injection). The product is manufactured to contain a 5% overfill of the lyophilized drug product in the vial, i.e. 15.75 mg desirudin. Administration instructions call for reconstitution of the lyophilized drug product with 0.5 mL of the 3% mannitol solution, followed by withdrawal of the entire contents of the vial for administration to the patient. The 5% overfill of the lyophilized powder in the vial, compensates for the small amount of reconstituted solution that remains behind in the vial and syringe, allowing for administration of the required 15 mg of desirudin.

B. Description of How the Drug Product is Intended to be Used

The recommended dose is 15 mg, administered subcutaneously twice daily for nine to twelve days.

C. Basis for Approvability or Not-Approval Recommendation

From the CMC perspective, this application may be approved since the drug product will meet the required quality standards that will make it as safe and effective as the drug tested in clinical trials.

Since the original submission, the following major approvability issues have been resolved

1) In the original submission, the biological activity of the drug product, as determined by the fibrin clot assay, was consistently reported to be [redacted] higher in the commercial batches than in the clinical batches, although both products were formulated to contain the same amount of drug substance. Since these data suggest a superpotent product, compared to the clinical trial batches, the applicant was requested to provide an explanation of the bioassay results. In response, the applicant has provided evidence that the activity of clinical batches was measured against the 1st WHO antithrombin standard (prepared in the 1970's), while the commercial-scale batches were measured

against the WHO antithrombin standard prepared in 1991. Data linking the activity of these standards has been provided, demonstrating that when the commercial-scale and clinical batches are measured against the same WHO standard, their activities fall in the same range.

2) Administration of the recommended 15 mg dose requires the removal of the entire (0.5 mL) reconstituted solution from the vial, which is a departure from the USP recommendation that each vial be filled with a volume in slight excess of the volume that is to be withdrawn. Consequently, the applicant was requested to demonstrate that the proper dose (15 mg desirudin) could be reproducibly withdrawn from the vial. Data were presented to demonstrate that in the laboratory setting the recommended reconstitution and administration procedure would reproducibly deliver 100-102% of the label dose. In consultation with the medical review team, it was concluded that comparable accuracy could be achieved in a clinical setting. When it was considered that the maximum possible "overdose" that could be administered would be 5% over label claim, and that possible "underdosing" would also be limited to only a few percent, it was concluded that the proposed reconstitution and administration procedures would have no adverse effect on the safety or efficacy of the product, and consequently, would be acceptable.

3) In consultation with the Office of Drug Safety, it was decided that the product label must indicate the actual amount of drug in the vial, not just the deliverable dose, i.e. it should indicate that the fill weight is 15.75 mg to deliver 15 mg.

III. Administrative

A. Reviewer's Signature

Marie Kowblansky, PhD
Review Chemist, HFD-180

Liang Zhou, PhD
Chemistry Team Leader, HFD-180

B. Endorsement Block

ChemistName/Date: Marie Kowblansky 3/3/03
ChemistryTeamLeaderName/Date Liang Zhou.
ProjectManagerName/Date Alice Kacuba

APPEARS THIS WAY
ON ORIGINAL

(H)

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

(5)

[redacted]

[redacted]

APPEARS THIS WAY
ON ORIGINAL

26-FEB-2003 FDA CDER EES Page 1 of 2
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application	: NDA 21271/000	Sponsor:	AVENTIS PHARMS
Org Code	: 180		F3 M3026
Priority	: 2S		KANSAS CITY, MO 641340708
Stamp Date	: 28-JUN-2000	Brand Name :	"IPRIVASK" INJECTION
PDUFA Date	: 04-APR-2003	Estab. Name:	
Action Goal	: 04-APR-2003	Generic Name:	DESIRUDIN
District Goal	: 03-FEB-2003	Dosage Form:	(INJECTION)
		Strength :	15 MG

FDA Contacts:	M. KOWBLANSKY	Review Chemist	(HFD-180)	301-827-7310
	L. ZHOU	Team Leader	(HFD-180)	301-827-1251

Overall Recommendation: ACCEPTABLE on 23-OCT-2002by J. D AMBROGIO(HFD-322) 301-827-9054

ACCEPTABLE on 12-JAN-2001by EGASM

Establishment : CFN : [redacted] FEI : [redacted]

DMF No: [redacted] AADA:

Responsibilities: [redacted]

Profile : SVL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 23-OCT-02
Decision : ACCEPTABLE
Reason : BASED ON PROFILE

Establishment : CFN : [redacted] FEI :

DMF No: [redacted] AADA:

Responsibilities: [redacted]

Profile : SVL OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 23-OCT-02
Decision : ACCEPTABLE
Reason : BASED ON FILE REVIEW

Establishment : CFN : 9611204 FEI : 3002807772
NOVARTIS PHARMA INC (SANDOZ)
LICHSTRASSE 35, ST. JOHANN SITE

Profile : CFN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 23-OCT-02
Decision : ACCEPTABLE
Reason : BASED ON FILE REVIEW

APPEARS THIS WAY
ON ORIGINAL

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

/s/

Marie Kowblansky
3/4/03 10:51:04 AM
CHEMIST

Liang Zhou
3/4/03 11:13:44 AM
CHEMIST

APPEARS THIS WAY ON ORIGINAL

This Page
is Missing
from the
Original
Approval Package

This section (stat review of stability) is not applicable.

/S/ 3-703

Alice Kacuba

This section (DMF review) is not applicable. Per Dr. Zhou, the only DMF is a [redacted] and there is not a written review needed for that DMF for this application.

/S/ 7-7-03

Alice Kacuba