CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-271

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-271 _____ _____

Drug Iprivask (desirudin) for Injection Applicant Avent s Pharmaceutical Products, Inc.

RPM Alice Kacuba Phone 7-7310

X505(b)(1)
☐505(b)(2) Reference listed drug _____

☐Fast Track ☐Rolling Review Review priority: X S ☐P

Pivotal IND(s) IND 34,046 — Injection

Application classifications:
Chem Class 2S
Other (e.g., orphan, OTC) _____

PDUFA Goal Dates:
Primary April 4, 2003
Secondary _____

Arrange package in the following order:

Indicate N/A (not applicable), X (completed), or add a comment.

GENERAL INFORMATION:

- User Fee Information: X User Fee Paid
  ☐ User Fee Waiver (attach waiver notification letter)
  ☐ User Fee Exemption

- Action Letter..... XAP ☐ AE ☐NA

- Labeling & Labels
  - FDA revised labeling and reviews..... X
  - Original proposed labeling (package insert, patient package insert) X
  - Other labeling in class (most recent 3) or class labeling..... X
  - Has DDMAC reviewed the labeling? ..... X Yes ☐ No
  - Immediate container and carton labels X
  - Nomenclature review .....tradename review..... X

- Application Integrity Policy (AIP) ☐ Applicant is on the AIP. This application ☐ is ☐ is not on the AIP. N/A
  - Exception for review (Center Director's memo)..... N/A
  - OC Clearance for approval..... N/A

◆ Status of advertising (if AP action) ☐ Reviewed (for Subpart H – attach review)	X Materials requested in AP letter
◆ Post-marketing Commitments	
Agency request for Phase 4 Commitments	X
Copy of Applicant's commitments	X
◆ Was Press Office notified of action (for approval action only)?	X Yes ☐ No
Copy of Press Release or Talk Paper	N/A
◆ Patent	
Information [505(b)(1)]	X
Patent Certification [505(b)(2)]	N/A
Copy of notification to patent holder [21 CFR 314.50 (i)(4)]	N/A
◆ Exclusivity Summary	X
◆ Debarment Statement	X
◆ Financial Disclosure	
No disclosable information	X
Disclosable information – indicate where review is located	N/A
◆ Correspondence/Memoranda/Faxes	X
◆ Minutes of Meetings	X
Date of EOP2 Meeting December 10, 1992	
Date of pre NDA Meeting N/A	
Date of pre-AP Safety Conference N/A	
Other Meetings: April 24, 1995, August 13, 1992, July 8, 1992, January 30, 1992, November 1, 1990	
◆ Advisory Committee Meeting	N/A
Date of Meeting	N/A
Questions considered by the committee	N/A
Minutes or 48-hour alert or pertinent section of transcript	N/A
◆ Federal Register Notices, DESI documents	N/A

CLINICAL INFORMATION:	Indicate N/A (not applicable), X (completed), or add a comment.
◆ Summary memoranda (e.g., Office Director's memo, Division Director's memo, Group Leader's memo)	X
◆ Clinical review(s) and memoranda	X
◆ Safety Update review(s)	Included in MORs
◆ Pediatric Information ☐ Waiver/partial waiver (Indicate location of rationale for waiver) ☐ Deferred Pediatric Page..... ☐ Pediatric Exclusivity requested? ☐ Denied ☐ Granted ☐ Not Applicable	Rule not in effect X N/A
◆ Statistical review(s) and memoranda	X
◆ Biopharmaceutical review(s) and memoranda.....	X
◆ Abuse Liability review(s) ..... Recommendation for scheduling	N/A N/A
◆ Microbiology (efficacy) review(s) and memoranda	N/A
◆ DSI Audits ..... X Clinical studies ☐ Bioequivalence studies	X

CMC INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- CMC review(s) and memoranda X
- Statistics review(s) and memoranda regarding dissolution and/or stability X
- DMF review(s) ..... N/A
- Environmental Assessment review/FONSI/Categorical exemption ..... N/A
- Micro (validation of sterilization) review(s) and memoranda X
- Facilities Inspection (include EES report) X
  Date completed ..... X Acceptable ☐ Not Acceptable
- Methods Validation ..... ☐ Completed X Not Completed

APPEARS THIS WAY
ON ORIGINAL

PRECLINICAL PHARM/TOX INFORMATION:

Indicate N/A (not applicable), X (completed), or add a comment.

- Pharm/Tox review(s) and memoranda X
- Memo from DSI regarding GLP inspection (if any) ..... N/A
- Statistical review(s) of carcinogenicity studies ..... N/A
- CAC/ECAC report ..... N/A

APPEARS THIS WAY
ON ORIGINAL

(N)

THIS SECTION WAS DETERMINED NOT TO BE RELEASABLE

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: 04-30-01

USER FEE COVER SHEET

See Instructions on Reverse Side Before Competing This Form

1. APPLICANT'S NAME AND ADDRESS

Aventis Pharmaceuticals Products Inc.
500 Arcola Road
Collegeville, PA 19426-0107

2. TELEPHONE NUMBER (*Include Area Code*)
(610) 454-3026

3. PRODUCT NAME
[redacted] (desirudin) Subcutaneous Injection

4. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. YES

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☐ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO _____
(APPLICATION NO. CONTAINING THE DATA).

5. USER FEE I.D. NUMBER.
3962

6. LICENSE NUMBER / NDA NUMBER
NDA 21-271

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (*Self Explanatory*)

☒ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE (*See item 7, reverse side before checking box.*)

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act (*See item 7, reverse side before checking box.*)

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act (*See item 7, reverse side before checking box.*)

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY (*Self Explanatory*)

FOR BIOLOGICAL PRODUCTS ONLY

☐ WHOLE BLOOD OR BLOOD COMPONENT FOR TRANSFUSION

☐ A CRUDE ALLERGENIC EXTRACT PRODUCT

☐ AN APPLICATION FOR A BIOLOGICAL PRODUCT FOR FURTHER MANUFACTURING USE ONLY

☐ AN "IN VITRO" DIAGNOSTIC BIOLOGICAL PRODUCT LICENSED UNDER SECTION 351 OF THE PHS ACT

☐ BOVINE BLOOD PRODUCT FOR TOPICAL APPLICATION LICENSED BEFORE 9/1/92

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☐ NO
(*See reverse side if answered YES*)

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Ronald F. Panner Ronald F. Panner	Sr. Director Worldwide Regulatory Affairs	6/19/2000

21.271
LD 3.14.03
RD 3.17.03

Item 13. Patent Information

1)	Patent number	US 4,801,576
2)	Date of expiration	January 31, 2006
3)	Type of patent	method of use
4)	Name of patent owner	Novartis Corporation
5)	U.S. representative	Aventis Pharmaceuticals Products Inc.

The undersigned declares that Patent No. 4,801,576 covers the formulation, composition, and/or method of use of Applicant's [redacted] (desirudin) product. This product is the subject of this application for which approval is being sought.

Signed: _____ Date: 3/13/03
Name: Ross J. Oehler
Title: U.S. Patent Operations and Department Administration
Aventis Pharmaceuticals Products Inc.

APPEARS THIS WAY
ON ORIGINAL

21.271
LD 3.14.03
RP 3-17-03

Item 13. Patent Information

1)	Patent number	US 4,745,177
2)	Date of expiration	May 17, 2005
3)	Type of patent	drug substance; drug product
4)	Name of patent owner	Novartis; UCP Ger.-Pharma
5)	U.S. representative	Aventis Pharmaceuticals Products Inc.

The undersigned declares that Patent No. 4,745,177 covers the formulation, composition, and/or method of use of Applicant's [redacted] (desirudin) product. This product is the subject of this application for which approval is being sought.

Signed: _____ Date: 3/13/03
Name: Ross J. Oehler
Title: U.S. Patent Operations and Department Administration
Aventis Pharmaceuticals Products Inc.

21-271
LD 3-14-03
RD 3-17-03

Item 14-Patent/Exclusivity Information

1)	Active Ingredient(s):	desirudin
2)	Strength(s):	15 mg lyophilized powder with an accompanying sterile, non-pyrogenic solvent (0.5 mL of 3% Mannitol in water for injection)
3)	Trademark:	[redacted]
4)	Dosage Form (Route of Administration):	Subcutaneous injection
5)	Application Firm Name:	Aventis Pharmaceuticals Products Inc.
6)	IND Number:	34,046
7)	NDA Number:	N/A
8)	Approval Date:	N/A
9)	Exclusivity -- date first ANDA could be submitted or approved and length of exclusivity period:	Pursuant to Sections 505(c)(3)(D), 505(j)(4)(D) or 527(a) of the Federal Food, Drug and Cosmetic Act, no ANDA may be approved with an effective date which is prior to 5 years after the date of approval of this application.
10)	Applicable patent numbers and expiration date of each:	US 4,745,177, expires May 17, 2005 US 4,801,576, expires January 31, 2006 US 5,733,874, expires March 31, 2015

11) To the best of our knowledge, each of the clinical investigations included in this application meets the definition of "new clinical investigation" set forth in 21 CFR 314.108(a).

A list of all published studies or publicly available reports of clinical investigations known to the applicant through a literature search that are relevant to the conditions for which we are seeking approval is attached. We have thoroughly searched the scientific literature and, to the best of our knowledge, the list is complete and accurate and, in our opinion, such published studies or publicly available reports do not provide a sufficient basis for the approval of the conditions for which we are seeking approval without reference to the new clinical investigation(s) in the application. The reasons that these studies or reports are insufficient are presented in the attachment as well.

EXCLUSIVITY SUMMARY for NDA # 21-271 SUPPL # N/A
Trade Name Iprivask™ Generic Name (desirudin) for Injection
Applicant Name Aventis Pharmaceuticals. Inc HFD-180
Approval Date April 4, 2003

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 /_X__/ NO /___/

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

5 years

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 #

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.)

YES /___/ NO /___/

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

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: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential tc 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 /_X__/ 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 /_X__/ 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 /_X__/

(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 /_X_/

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 /_X__/

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 # RH/E 23

Investigation #2, Study # RH/E 25

Investigation #3, Study # RH/E 28

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

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

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 #1, Study # RH/E 23

Investigation #2, Study # RH/E 25

Investigation #3, Study # RH/E28

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 # 34,046 YES /_X__/ NO /___/ Explain:

Investigation #2

IND # 34,046 YES /_X_/ NO /___/ Explain:

Investigation #3

IND # 34,046 YES /_X_/ 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?

N/A

(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 /_X__/

If yes, explain: _____

_____
Signature of Preparer
Alice Kacuba Date
Regulatory Health Project Manager

Signature of Division Director Date

cc:
Archival NDA in DFS
HFD-180/A.Kacuba
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

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

/s/

Alice Kacuba
4/4/03 03:08:32 PM

Robert Justice
4/4/03 03:13:36 PM

APPEARS THIS WAY
ON ORIGINAL

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA # : 21-271 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: (1st cycle) June 28, 2000 (2nd cycle) October 3, 2002 Action Date: April 4, 2003

HFD-180 Trade and generic names/dosage form: Iprivask (desirudin) for Injection

Applicant: Aventis Pharmaceuticals, Inc. Therapeutic Class: 2/S

Indication(s) previously approved: N/A

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: The prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism, in patients undergoing elective hip replacement surgery.

Is there a full waiver for this indication (check one)?

XX Yes: Please proceed to Section A.

☐ No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

tion A: Fully Waived Studies

Reason(s) for full waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
XX Too few children with disease to study
☐ There are safety concerns
☐ Other:_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for partial waiver:

☐ Products in this class for this indication have been studied/labeled for pediatric population
☐ Disease/condition does not exist in children
☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval
☐ Formulation needed
☐ Other:_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

tion D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

The June 28, 2000 cover letter requests a full waiver from conducting pediatric studies. The May 14, 2001 Medical Officer Review (1st cycle) recommended a full waiver because elective hip replacement is rare in the pediatric population. However, due to the recent court activities regarding the rule, the Approval letter does not include the waiver language .

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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

/s/

Alice Kacuba
4/4/03 03:37:19 PM
Reviewed by Kathy Robie-Suh, MOTL

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

/S/ 5-8-01

NDA Number: N 021271
Trade Name: [redacted] (DESIRUDIN) 15MG
Generic Name: DESIRUDIN
Supplement Number. 000 **Supplement Type:** N
Dosage Form:
Regulatory Action: UN **Action Date:** 6/28/00
COMIS Indication: PROPHYLAXIS OF DEEP VEIN THROMBOSIS/WHICH MAY LEAD TO PULMONARY EMBOLISM/IN PATIENTS UNDERGOING ELECTIVE HIP REPLACEMENT SURGERY

Indication #1: Prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism, in patients undergoing elective hip replacement surgery
Label Adequacy: Adequate for all pediatric age groups
Formulation Needed: No new formulation is needed
Comments (if any) This compound is not an NME so the 12/2/98 Pediatric Rule does not apply. However, since the proposed indication rarely occurs in children, a waiver was recommended in the Medical Officer's Review #1.

Lower Range	Upper Range	Status	Date
Adult	Adult	Waived	

Comments: See previous comment.

This page was last edited on 5/8/01

Signature /S/ _____ 5-8-01 Date

Item 16: Debarment Certification

As required by Section 306(k)(1) of the Generic Drug Enforcement Act [21 U.S.C. 335a(k)(1)], we hereby certify that. in connection with this application, Aventis did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the act.

APPEARS THIS WAY
ON ORIGINAL

For this application, according to the sponsor in Volume 1 on pages 17-75, there were no financial arrangements with any of the sponsors.

/S/ 3-10-03

Alice Kacuba

APPEARS THIS WAY
ON ORIGINAL

There was no Advisory Committee Meeting for this application.

/S/ 3703

Alice Kacuba

APPEARS THIS WAY
ON ORIGINAL

This section (FR notices and DESI notices) is not applicable for this application

S 3-7-03

Alice Kacuba

APPEARS THIS WAY
ON ORIGINAL

This section (EER) is covered by Dr. Kowblansky's March 4, 2003 cmc review.

3-14-03

Alice Kacuba

APPEARS THIS WAY
ON ORIGINAL

Division Director Review of a New Drug Application

NDA: 21-271
Drug: Iprivask? (Desirudin for Injection)
Applicant: Aventis Pharmaceuticals, Inc.
Date: April 4, 2003

Iprivask is a specific inhibitor of human thrombin with a protein structure that is similar to that of hirudin, the naturally occurring anticoagulant produced by the medicinal leech. Iprivask is expressed in yeast by recombinant DNA technology and differs from hirudin in that it lacks a sulfate group on Tyr-63. This new drug application seeks approval of Iprivask for the indication of "prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism, in patients undergoing elective hip replacement therapy." The Division summary review was completed by Dr. Kathy Robie-Suh on March 31, 2003. This review will summarize the efficacy and safety data that support approval.

Efficacy

Iprivask was studied in two multicenter, randomized, controlled efficacy trials and in one multicenter, randomized, controlled, double-blind, dose-finding study. In all studies patients were undergoing total hip replacement surgery and Iprivask was administered prior to surgery and for 8-12 days postoperatively. In study RH/E28 Iprivask 15 mg SC every 12 hours was compared to unfractionated heparin (UFH) 5000 IU SC every 8 hours. A total of 445 patients were randomized and 436 were treated. Eighty-five of the treated patients were excluded from the analysis of evaluable patients, primarily because a venogram was not done or because the reading was inadequate. In this study Iprivask significantly reduced the number of venous thromboembolic events (VTE) in both the evaluable and intent-to-treat (ITT) analyses. In the evaluable patient analysis, VTE's occurred in 13/174 (7.5%) of patients on Iprivask vs. 41/177 (23.2%) of patients on UFH ($p<0.001$). In the ITT analysis VTE's occurred in 13/225 (5.8%) of the Iprivask patients vs. 42/220 (19.1%) of the UFH patients ($p<0.0001$). When considering only proximal DVT's, Iprivask also significantly reduced the number of events. In the evaluable patient analysis proximal DVT's occurred in 6/174 (3.4%) of the Iprivask patients vs. 30/220 (13.6%) of the UFH patients ($p<0.001$). In the ITT analysis proximal DVT's occurred in 6/225 (2.7%) of Iprivask patients vs. 30/220 (13.6%) of the UFH patients ($p<0.0001$).

In study RH/E25 Iprivask 15 mg SC every 12 hours was compared to enoxaparin sodium 40 mg SC every 24 hours. A total of 2079 patients were randomized and 2049 were treated. In the evaluable analysis 508 treated patients were excluded, primarily because a venogram was not done or the reading was inadequate. The results are shown in the tables on the next page. Major VTE includes proximal DVT, PE, or death. Total VTE includes DVT, PE, or death considered to be thromboembolic in origin.

Evaluable Patient Analysis: Study RH/E25

	Iprivask	Enoxaparin	
	N=773	N=768	
	N (%)	N (%)	p value
Total VTE	145 (18.8)	197 (25.7)	p<0.001
Major VTE*	39 (4.9)	61 (7.9)	p<0.02
Proximal DVT	36 (4.5)	59 (7.7)	p=0.012

*denominator: Iprivask 802; Enoxaparin 785

ITT Analysis: Study RH/E25

	Iprivask	Enoxaparin	
	N=1043	N=1036	
	N (%)	N (%)	p value
Total VTE	145 (13.9)	199 (19.2)	p=0.001
Major VTE*	39 (3.7)	61 (5.9)	p=0.024
Proximal DVT	36 (3.5)	59 (5.7)	p=0.012

*denominator: Iprivask 802; Enoxaparin 785

In study RH/E23 patients were randomized to three Iprivask dose levels (10 mg, 15 mg, 20 mg SC every 12 hours) or to UFH 5000 units SC every 8 hours. A total of 1119 patients were randomized. In the evaluable population analysis, VTE's occurred in 51/213 (23.9%) in the 10 mg dose group, 36/196 (18.4%) in the 15 mg dose group, 37/209 (17.7%) in the 20 mg dose group, and 75/219 (34.2%) in the UFH group. The 15 mg and 20 mg dose levels were significantly superior to heparin. An ITT analysis was not performed.

Safety

Hemorrhage is the most common adverse event and is summarized in the table below. Any hemorrhage includes hematomas. Serious hermorrhage is defined as perioperative transfusion requirements in excess of 5 units, transfusion requirements up to post-operative day 6 exceeding 7 units, or total blood loss up to day 6 exceeding 3500 mL. Major hemorrhage is defined as overt bleeding with a fall in hemoglobin ?2 g/dL, or transfusion of 2 or more units outside the perioperative period, or retroperitoneal, intracranial, intraocular, intraspinal, or prosthetic joint hemorrhage.

Hemorrhage

	Iprivask (N=1561)	Heparin (N=501)	Enoxaparin (N=1036)
Any Hemorrhage	464 (30%)	111 (22%)	341 (33%)
Serious Hemorrhage	41 (3%)	15 (3%)	21 (2%)
Major Hemorrhage	13 (<1%)	0 (0%)	2 (<1%)

Other adverse events that occurred at ?2% incidence in the Iprivask treated patients and that were remotely, possibly, or probably related to Iprivask are shown in the table below.

	Iprivask (N=1561)	Heparin (N=501)	Enoxaparin (N=1036)
Injection site mass	56 (4%)	32 (6%)	7 (<1%)
Wound secretion	59 (4%)	23 (5%)	34 (3%)
Anemia	51 (3%)	11 (2%)	37 (4%)
Deep Thrombophlebitis	24 (2%)	41 (8%)	22 (2%)
Nausea	24(2%)	5 (<1%)	10 (<1%)

Related adverse events occuring at a frequency <2% but >0.2% include thrombosis, hypotension, leg edema, fever, decreased hemoglobin, hematuria, dizziness, epistaxis, vomiting, impaired healing, cerebrovascular disorder, leg pain, and hematemesis. Allergic reactions were reported in 2% of patients receiving Iprivask.

Conclusions

Study RH/E28 demonstrated that Iprivask 15 mg SC every 12 hours was superior to unfractionated heparin (UFH) 5000 IU SC every 8 hours for the endpoints of total VTE's and proximal DVT's. Study RH/E25 demonstrated that Iprivask 15 mg SC every 12 hours was superior to enoxaparin sodium 40 mg SC every 24 hours for the endpoints of total VTE, proximal DVT, and major VTE. Study RH/E23 demonstrated that the Iprivask dose levels of 15 mg and 20 mg SC every 12 hours were superior to UFH 5000 units SC every 8 hours for the endpoint of VTE's. Although heparin had a lower rate of any hemorrhage, the rates of serious and major hemorrhage were similar for the three treatments. These results warrant approval of Iprivask for the proposed indication.

{See appended electronic signature page}

Robert L. Justice, M.D., M.S.
Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Robert Justice
4/4/03 12:51:55 PM
MEDICAL OFFICER

Division of Gastrointestinal & Coagulation Drug Products

PROJECT MANAGER'S REVIEW

Application Number: NDA 21-271

Name of Drug: [redacted] [desirudin [redacted] for injection]

Sponsor: Aventis Pharmaceutical Products, Inc.

Material Reviewed

Submission Date: June 28, 2000

Receipt Date: July 14, 2000

Labeling Submitted: Immediate container label for [redacted] lyophilized powder for injection, immediate container label for Solvent for [redacted] and 2-count and 10-count carton labels

Background and Summary Description

NDA 21-271 for [redacted] [desirudin [redacted] for injection] was submitted June 28, 2000 for the prevention of deep vein thrombosis, which may lead to pulmonary embolism, in patients undergoing elective hip replacement surgery. The drug product is supplied in 15 mg vials containing lyophilized powder for injection accompanied by an ampule containing 0.5 mL of Solvent for [redacted]. The sponsor is proposing to market the product in 2-count and 10-count cartons. Color mock-ups of the immediate container labels for the lyophilized powder for injection, Solvent for [redacted], and the 2-count and 10-count cartons were submitted in [redacted] the NDA. Labeling comments concerning these components were provided by OPDRA in their review dated November 13, 2000 and in CMC Review #1 dated April 11, 2001.

Review

I. Immediate Container

A. [redacted] Vial Label

1. The name and place of business of the manufacturer, packer or distributor is required per 21 CFR 201.1. This information is lacking.

2. The statement "Rx only" is required per FDAMA 1997. This information is lacking.

3. The names and quantities of inactive ingredients are required per 21 CFR 201.100 (b)(5)(iii). This information is lacking.

B. Solvent for —— Ampule Label

1. The name and place of business of the manufacturer, packer or distributor is required per 21 CFR 201.1. This information is lacking.

2. The statement "Rx only" is required per FDAMA 1997. This information is lacking.

II. 2-Count and 10-Count Carton Labels

A. The statement "Rx only" is required per FDAMA 1997. This information is lacking.

B. The quantities of inactive ingredients in the —— Vial (magnesium chloride and sodium hydroxide) are required per 21 CFR 201.100 (b)(5)(iii). This information is lacking.

Conclusions

In the action letter for this application, the firm will be requested to submit revised immediate container and carton labeling including the revisions described above as well as those requested by OPDRA and in CMC Review #1.

cc:
NDA 21-271
HFD-180/B.Strongin
HFD-180/Reviewers & Team Leaders

Drafted by: BKS/May 7, 2001
Final: BKS/May 7, 2001

PM REVIEW

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/s/

Brian Strongin
5/10/01 09:48:52 AM
CSO

Lilia Talarico
5/10/01 06:30:03 PM
MEDICAL OFFICER

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Number of Pages Redacted 25

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Draft Labeling
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Approved Countries

Countries	Indication	Date	Dosage(s)
European Union	Prevention of deep venous thrombosis in patients undergoing elective hip and knee replacement surgery.	July 9, 1997	15 mg b.i.d.
Australia	Prevention of venous thromboembolism after elective hip replacement.	Nov 11, 1996	15 mg b.i.d.
New Zealand	Prevention of thromboembolic complications after orthopaedic surgery	Nov 28, 1996	15 mg b.i.d.
South Africa	Prevention of deep vein thrombosis in elective hip replacement surgery, in patients over 50kg body mass.	July 24, 1998	15 mg b.i.d.
Switzerland	Prevention of thromboembolic complications after orthopaedic surgery	Dec 5, 1997	15 mg b.i.d.
Czech Republic	Prevention of venous thromboembolism after hip and knee replacement.	June 16, 1999	15 mg b.i.d.
Brazil	Prevention of venous thromboembolism after elective hip replacement.	Aug 16, 1999	15 mg b.i.d.
Hungaria	Prevention of venous thromboembolism after elective hip replacement.	Sept 9, 1999	15 mg b.i.d.
Norway	Prevention of venous thromboembolism after elective hip replacement.	July 1, 1999	15 mg b.i.d.
Uruguay	Prevention of venous thromboembolism after elective hip replacement.	Aug 27, 1999	15 mg b.i.d.

Submissions

Countries	Indication	Date	Dosage(s)

(P)

Number of Pages Redacted 61

❖❖❖

Draft Labeling
(not releasable

This section (Abuse Potential) is not applicable.

/S/ 3-7-03

Alice Kacuba

This section (microbiology review for efficacy) is not applicable for this application.

/S/

3-703

Alice Kacuba

Office of Drug Safety

MEMO

To: Robert Justice, MD
Director, Division of Gastro-Intestinal and Coagulation Drug Products
HFD-180

From: Kevin Dermanoski, RPh
Safety Evaluator, Division of Medication Errors and Technical Support
HFD-420

Through: Denise P. Toyer, PharmD
Team Leader, Division of Medication Errors and Technical Support
HFD-420

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

CC: Alice Kacuba
Project Manager, Division of Gastro-Intestinal and Coagulation Drug Products
HFD-180

ate: March 10, 2003

Re: ODS Consult 00-208-3; Iprivask (Desirudin for Injection) 15 mg; NDA 21-271

This memorandum is in response to the February 28, 2003 request from your Division to re-review the proposed proprietary name "Iprivask."

The Division of Medication Errors and Technical Support has not identified any additional proprietary or established names that have the potential for confusion with "Iprivask" since we conducted our review on November 12, 2002 (ODS Consult 00-0208-1). Therefore, we have no objections to the use of this proprietary name. DMETS refers to the labeling, packaging and safety related issues identified in the February 5, 2003 review (ODS Consult 00-0208-2).

ODS considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before NDA approval will rule out any objections based upon approvals of other proprietary and/or established names from this date forward.

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

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/s/

Kevin Dermanoski
3/11/03 09:52:00 AM
PHARMACIST

Denise Toyer
3/12/03 09:49:42 AM
PHARMACIST

Jerry Phillips
3/17/03 12:13:13 PM
DIRECTOR

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-271

INFORMATION REQUEST LETTER

Aventis Pharmaceuticals Inc.
Attention: Mary E. Elicone, R.Ph.
200 Crossing Boulevard
Mail stop: BX2-206-B
Bridgewater, NJ 08807-0890

Dear Ms. Elicone:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Iprivask™ (desirudin) for Injection.

As a post-marketing commitment, please commit to conducting a clinical study in hepatically impaired patients to provide safety information and an appropriate dosing regimen for those patients. Your commitment should be in the following format:

Description: A clinical study in hepatically impaired patients to provide safety information and an appropriate dosing regimen for those patients

Protocol Submission:	Within X months of the date of this letter
Study Start:	Within X months of the date of this letter
Final Report Submission:	Within X months of the date of this letter

We need your prompt written response to continue our evaluation of your NDA.

If you have any questions, call Alice Kacuba, MSN, RN, RAC, Regulatory Health Project Manager, at (301) 827-1602.

Sincerely,

{See appended electronic signature page}

Julieann DuBeau, MSN, RN
Chief, Project Management Staff
Division of Gastrointestinal & Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Julieann DuBeau
3/11/03 03:41:33 PM

APPEARS THIS WAY
ON ORIGINAL

This section (Press Office) is not applicable for this application. No Talk Paper is needed for this application.

/s/ 3-703

Alice Kacuba

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Aventis Pharmaceuticals Inc.	3/14/2003
TELEPHONE NO. (Include Area Code)	**FACSIMILE (FAX) Number *(Include Area Code)***
(908) 304-7000	(908) 304-6560
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):	**AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE**
200 Crossing Blvd. Bridgewater, N.J. 08807-0890	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) NDA 21-271

ESTABLISHED NAME (e.g., *Proper name, USP/USAN name*)	PROPRIETARY NAME (*trade name*) IF ANY	CODE NAME (*If any*)
desirudin	Iprivask™	RPR205511/CGP39393

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*)	DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
n/a	Single dose (15 mg) lyophilized powder	15 mg	Subcutaneous injection

(PROPOSED) INDICATION(S) FOR USE:
Iprivask™ is indicated for the prevention of deep vein thrombosis, which may lead to pulmonary embolism, in patients undergoing elective hip replacement surgery.

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION (check one) ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY, MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Response to FDA Request

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED N/A THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

see NDA 21-271 submitted on June 28, 2000

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

see NDA 21-271 submitted on June 28, 2000

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☐	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50 (d)(1), 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50 (e)(2)(i), 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50 (d)(2), 21 CFR 601.2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50 (d)(3), 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50 (d)(4))
☐	8. Clinical data section (e.g., 314.50 (d)(5), 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50 (d)(5)(vi)(b), 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50 (d)(6), 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50 (f)(1), 21 CFR 601.2)
☐	12. Case reports forms (e.g., 21 CFR 314.50 (f)(2), 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355(b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (k)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* Post-Approval Commitment

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Mellicone	Mary E. Elicone, RPh Global Regulatory Coordinator (Aventis)	3/14/2003

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
200 Crossing Boulevard Mailstop: BX2-206-B Bridgewater, NJ 08807-0890	(908) 304-6253

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Dr., Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it desplays a currently valid OMB control number.

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: March 26, 2003

To: Mary E. Elicone, RPh Global Regulatory Coordinator	**From:** Alice Kacuba, MSN, RN, RAC
Company: Aventis Pharmaceuticals, Inc.	Division of Gastrointestinal and Coagulation Drug Products
Fax number: 908-304-6560	**Fax number:** 301-443-9285
Phone number: 908-304-6253	**Phone number:** (301) 827-1602 or 7310

Subject: NDA 21-271

Total no. of pages including cover: 21

Comments: As discussed with you on the phone, the Division is sending Aventis the FDA revised labeling for NDA 21-271. See attached package insert text and text for cartons and labels. I have indicated requested deletions as strikeout text and requested additions as double underline text. There are several places where I have indicated as "Note to firm" where we would like you to insert additional information. Please review and respond as a written amendment to the NDA. The written response should include a mocked up version showing any revisions made. If there are any points that need further discussion, the tcon remains scheduled for Monday, March 31, 2003 from 4-5 PM. Please provide a phone number where we can call you at for the tcon. For the tcon to be most beneficial for both parties, it would be optimal if we could have your revisions prior to the tcon.

/S/

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/s/

Alice Kacuba
3/26/03 02:45:04 PM
CSO

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

DATE: March 31, 2003

To: Mary E. Elicone, RPh Global Regulatory Coordinator	**From:** Alice Kacuba, R.N., MSN, RAC
Company: Aventis Pharmaceuticals, Inc.	Division of Gastrointestinal and Coagulation Drug Products
Fax number: 908-304-6560	**Fax number:** 301-443-9285
Phone number: 908-304-6253	**Phone number:** (301) 827-1602 or 7310

Subject: NDA 21-271

Total no. of pages including cover: 2 3

/S/

Comments: Attached is the FDA attendee list for the tcon at 4 PM

Documents to be mailed: ☐ YES ☑ NO

Dr. Robert L. Justice; Division Director
Dr. Joyce Korvick; Deputy Division Director
Dr. Kathy Robie-Suh; Medical Team Leader, Hematology
Dr. Ruyi He; Medical Reviewer
Dr. Liang Zhou; Chemistry Team Leader
Dr. Marie Kowblansky; Chemistry Reviewer
Dr. Albert Chen, Biopharmaceutics Reviewer
Dr. Jasti Choudary; Supervisory Pharmacologist
Ms. Alice Kacuba; Regulatory Health Project Manager

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/s/

Alice Kacuba
3/31/03 12:49:22 PM
CSO

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

Date: March 31, 2003

From: Kathy M. Robie-Suh, M.D., Ph.D.
Medical Team Leader, Hematology, HFD-180

Subject: Summary Review
NDA 21-271 Iprivask™ (desirudin)
Resubmission, October 3, 2002

To: Director, Division of Gastrointestinal and Coagulation Drug Products (HFD-180)

Background and Rationale:
Desirudin (Iprivask) is a selective thrombin inhibitor being developed for antithrombotic indications. Chemically, it is a 65 amino acid polypeptide (mol. wt. 6963.52), rDNA-derived anticoagulant identical to naturally occurring hirudin (leech anticoagulant), except that it lacks a sulfate group on Tyr-63. On June 28, 2000 the sponsor submitted an NDA supporting marketing of desirudin for the [redacted], with proposed dosing of 15 mg desirudin administered twice daily by subcutaneous (sc) injection initiated preoperatively and continued post-operatively for 9-12 days.

The chemistry, manufacturing and controls (CMC) information, the non-clinical pharmacology and toxicology studies, the clinical pharmacology and biopharmaceutics information and the clinical studies supporting the indication and marketing approval were reviewed during the first review cycle. (See CMC reviews by J. Brown, 3/26/01 and M. Kowblansky, 4/11/01; Microbiology Review by N. Sweeney, 3/29/01; Pharmacology Review by Y. Chopra, 5/4/01; Clinical Pharmacology and Biopharmaceutics Review by S. Roy, 3/19/01; Medical Officer's Review by A. Farrell, 5/14/01; Statistical Review by M. Rashid, 4/25/01). Findings of these reviews were summarized in my Medical Team Leader Review Memorandum dated 5/11/01).

Briefly, to support the desired indication the sponsor submitted two main adequate and well-controlled clinical trials (RH/E28 and RH/E25) and a dose-finding trial (RH/E23). These studies enrolled a total of 3643 patients, 2109 treated with desirudin, 498 with unfractionated heparin (UFH), and 1036 with enoxaparin. Safety information for desirudin was derived from the three efficacy trials plus 2 additional studies (2159 patients) for prevention of DVT. Mean age in the studies ranged from 63 to 71 years, about 57-69% of patients were women. About 75-79% of patients were evaluable for

primary efficacy outcome. Efficacy results for the three controlled trials are shown in the following table:

Efficacy Results for Controlled Clinical Efficacy Studies

Event (number, %)	Study RH/E23 (N=1203[a])					Study RH/E25 (N=2086)			Study RH/E28 (N=452)		
	Desirudin 10mg	Desirudin 15mg	Desirudin 20mg	Heparin	p-value	Desirudin 15mg	Enoxaparin	p-value	Desirudin 15mg	Heparin	p-value
Efficacy Evaluable Population:											
VTE	51/213 (23.9%)	37/196 (18.9%)	38/209 (18.2%)	75/219 (34.2%)	#	39/802 (4.86%)	60/785 (7.64%)	0.018	13/174 (7.5%)	41/177 (23.2%)	0.0001
Proximal DVT	18/213 (8.5%)	6/196 (3.1%)	5/209 (2.4%)	43/219 (19.6%)		36/802 (4.49%)	59/785 (7.52%)	0.0088	6/174 (3.4%)	29/177 (16.4%)	<0.001
All-Patients-Treated-and-Operated Population:											
VTE	51/283 (18.0%)	37/277 (13.4%)	38/282 (13.5%)	75/278 (27.0%)	@	39/1042 (3.74%)	60/1036 (5.79%)	0.031	13/225 (5.78%)	41/220 (18.6%)	<0.0001
Proximal DVT	18/283 (6.4%)	6/277 (2.2%)	5/282 (1.8%)	43/278 (15.5%)	@	36/1042 (3.45%)	59/1036 (5.69%)	0.016	6/225 (2.67%)	29/220 (13.2%)	<0.0001

sponsor's p-values: VTE: 20mg vs. heparin, 0.0001; 15mg vs. heparin, 0.0002; 10mg vs. heparin, 0.0113.
@ personal communication, 2-sided p-values by Fisher's exact, FDA Biometrics, M.Fan
VTE: 20mg vs. heparin, <0.0001; 15mg vs. heparin, <0.0001; 10mg vs. heparin, 0.012
Proximal DVT: 20mg vs. heparin, <0.0001; 15mg vs. heparin, <0.0001; 10mg vs. heparin, 0.0006.

Reviewer's original table, from page 13 of Medical Team Leader's memo, 5/11/01

The major safety concern for desirudin is bleeding, particularly for patients with spinal-epidural anesthesia, as has been found for other anticoagulants. In the clinical trials about 0.8% of patients treated with desirudin 15mg had major bleeding. Desirudin is renally cleared and dose-adjustment is required in patients having moderate or severe renal impairment. Desirudin is classified as a Pregnancy Category C drug, because of congenital malformation in rat and rabbit teratogenicity studies.

The NDA submission was found to be approvable (letter dated May 14, 2001) pending resolution of several issues with regard to Chemistry, Manufacturing and Controls (CMC), Nonclinical Pharmacology and Toxicology and Clinical. Also, the trade name initially proposed by the sponsor, [redacted] was disapproved by Office of Post-Marketing Drug Risk Assessment (OPDRA), because there is potential confusion with two sound-alike, look alike names that already exist in the U.S. marketplace (i.e., Prevacid and Norvasc)(OPDRA review dated 11/13/00).

Current Review Cycle:
In this resubmission dated October 3, 2002 the sponsor has responded in full to the Division's May 14, 2001 approvable letter.

The approvability issues and the sponsor's responses and Division's conclusions during this review cycle are summarized below:

I. Chemistry, Manufacturing and Control approvability issues: CMC issues were delineated in a Discipline Review Letter to the sponsor dated Apri. 16, 2001. Briefly, the sponsor was requested to do the following:

Regarding the drug substance:

- Characterization: Identify and characterize the two unknown identified by HPLC
- Method of Manufacture:
  - Submit a COA of the [redacted] used to prepare the [redacted]
  - [redacted]
  - Submit an executed batch record for the drug substance.
- Process Controls:
  - Add in-process controls for purity in the following steps in the purification process: [redacted]

- Add in-process control for bioburden at step involving

- Regulatory Specifications/Analytical Methods:
  - Revise the specification for "Other related substances" to include only bioactive molecules.
  - Demonstrate how is detected and quantitated.
  - Classify the desirudin variants that have no biological activity as product-related impurities and implement an impurity specification to include these variants.
  - Base specifications for "Other Related Substances" and "Total Impurities" on previous lots used in Phase III trials and currently manufactured batches and submit a statistical evaluation in support of each specification.
  - Revise the limit of the specification for "Total Viable Aerobic Count" and "Yeast Proteins" to reflect values obtained in manufactured lots.
  - Perform a comparison of the peptide map of native protein to qualitatively assess the presence of correct disulfide bonds (or, alternatively, alalyze both unreduced and reduced proteins).
- Drug Substance Stability: Submit 18-month stability data for lots 198, 298, and 398 and 12-month stability data for lots 699. 799 and 899; clarify whether batches 198 and 298 (which failed stability at 12-months when stored at –20°C) are intended for commercial distribution.

Regarding the drug product:

- Components and Composition: Provide additional information regarding the experiments that were conducted to determine the amount of desirudin that can be withdrawn from a vial containing reconstituted solution.
- Methods of Manufacturing:
  - Provide a statement that no reprocessing is planned without prior Agency approval.
  - Provide data to support the conclusion that the bulk drug solution may be stored for up to 12 hours without
  - Perform an in-process test for desirudin content on the bulk drug prior to and into vials.
  - Provide batch records for the manufacture of the drug product and the mannitol diluent.
- Clinical Batches:
  - Explain why the biological activity, as determined by the fibrin clot assay, is consistently higher in the commercial-scale batches than in the clinical batches.
  - Provide stability data for desirudin batches that were used in clinical trials to

demonstrate how much of the active was actually administered in the clinical trials. (Desirudin used in the clinical trials was formulated with mannitol which is less stable than desirudin formulated with magnesium chloride that was used in some of the stability studies.

- Regulatory Specifications:
  - Revise the drug product specifications to include only biologically active desirudin derivatives as "related substances". Classify compounds with no or very low biological activity as "product-related impurities", set individual and total limits for all known impurities and related substances and specify a limit for other unidentified impurities.
  - Revise the proposed — limit for total related substances specification to reflect the much lower levels observed in clinical and commercial-scale batches. Similarly, lower the upper limit for individual related substances.
  - Toxicologically qualify impurity · ——————— since there is no indication how much of this impurity was present in the clinical batches.
  - Lower the total dimer specification limit to reflect levels that have been observed in clinical and commercial-scale batches.
  - Add peptide mapping to the registration specifications for the drug product and to the stability protocol.
  - Revise the proposed —— specification for absorbance to reflect the much lower levels observed in clinical and commercial scale batches.
  - Revise the proposed / minute specification for dissolution times to reflect the much lower ——— levels observed for all clinical and commercial-scale batches were consistently below — seconds.
  - Assign unique identifying numbers to each of the analytical methods used for product release and stability testing. The numbering system should have provisions for modifying the method number every time the method is modified.
  - Regarding the HPCL method for desirudin: Provide evidence that for a substantially degraded sample of the drug product (obtained under stress conditions) the chromatographic conditions allow for complete resolution of desirudin from the impurities identified above and from any unidentified impurities that may form; provide a chromatogram identifying where all the known process-related impurities and degradation products of desirudin elute under the chromatographic conditions and identify all recurring unidentified impurities present and provide retention times relative to desirudin; for all known impurities which are not detected by the HPLC method, develop an alternate method and apply it on a routine basis for product release and stability testing.
  - Container/closure system: Explain why the desirudin drug product is packaged in clear glass vials though your stability studies concluded that the product needs to be protected from light; ——————— ———
  - Microbiology:
    - Submit a microbial retention validation report for the ——————— — used to — ——— (desirudin) bulk solution.
    - Determine the heat resistance of the] —— in the 3% mannitol solution (Mannitol Solvent for ——

- Provide a study report including methodology and data supporting the proposed [redacted]
- Perform endotoxin testing at the initial and expiry time points for Mannitol Solvent for [redacted]

- Stability: Indicate at what temperature the reconstituted solutions were stored during the 24-hour investigation of their solution stability: Revise the post-approval stability commitment to test the mannitol diluent at [redacted]

Comments:
The sponsor's responses to CMC issues have been reviewed by FDA Chemistry. (See chemistry reviews by M. Kowblansky, 12/23/02 and 3/4/03, and J. Brown, 2/27/03). The sponsor was found to have adequately addressed all the CMC issues with regard to the drug substance and drug product, with recommendations that the sponsor be informed that:

- A shelf-life of 24-months for the drug substance stored at –20°C is granted instead of a retest period, and
- The sponsor should include a method identifier (e.g., alphanumeric code number) on the drug substance specification sheet.

With regard to labeling, Chemistry review, in consultation with the Office of Drug Safety, 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.

Microbiology Review (P. Stinavage, 3/3/03) found that the sponsor's responses to all microbiology issues were satisfactory and provided adequate sterility assurance.

II. Nonclinical Pharmacology and Toxicology approvability issue:
The sponsor was requested to conduct a subacute, subcutaneous, 4-week toxicity study in rhesus monkeys and submit its full report for review and evaluation. (This study had been previously requested in letters to the sponsor dated September 1, 2000 and December 15, 2000).

Comments: The sponsor submitted the requested study and it was reviewed. (See FDA Pharmacology review, Y. Chopra, 2/28/03). Identified target organs of toxicity were liver, site of injection and kidneys and 0.5 mg/kg/day was considered as no effect dose. Recommendations were made for changes in the proposed labeling under section **"PRECAUTIONS: Animal Pharmacology and Toxicology:** *General Toxicity"* and under section "**PRECAUTIONS: Pregnancy:** *Teratogenic Effects*".

III. Clinical approvability issues: Clinical approvability issues included:

- Address safety concerns regarding the proposed 2-count carton. The carton was labeled as ——— 15 mg and it was felt that it may be mistaken that the total content of the 2-count carton is 15 mg.

  In response the sponsor revised the content statement on the 2-count carton to read "**Two (2)** x 15 mg Single Dose Vials" for the 2-count carton and "**Ten (10)** x 15 mg Single Dose Vials" for the 10-count cartons.

- Submit an alternative proposed proprietary name. ——— was deemed unacceptable because of potential for confusion with existing sound-alike, look alike names (i.e., Prevacid and Norvasc).

- Provide a safety update

- Submit revised draft labeling incorporating changes recommended in the approvable letter.

- Submit revised immediate container and carton labeling incorporating changes specified in the approvable letter.

Comments:
The clinical responses were reviewed by FDA Medical Reviewer (R. He, 3/7/03). The sponsor's revised wording for the 2-count carton label was found to be acceptable from a clinical viewpoint. The sponsor's new proposed proprietary name, IPRIVASK, has been found to be acceptable by the Division of Medication Errors (consult review 12/5/02). The information in the safety update generally was consistent with the known safety profile of desirudin (reviewed in the original NDA review, A. Farrell, 5/14/01)

The sponsor provided revised draft labeling which incorporated most of the changes requested by the Division in the approvable letter. Important additional changes to the revised labeling that are recommended based on FDA clinical review during this cycle include:

- In the **CLINICAL TRIALS** section: The presentation of information about race, age and gender should be simplified for each of the pivotal trials. (Exact wording provided in Medical Officer's Review).
- In the **CLINICAL TRIALS** section: In the approvable letter the Division requested that the sponsor revise the presentation of the study results to present results based on the ITT population rather than the evaluable population, as the sponsor had proposed. In the resubmission the sponsor retains the efficacy analysis of "Evaluable Patients" citing that that is a more conservative presentation of the results (i.e., in the evaluable analyses both treatment groups have higher event rates than would be apparent from the ITT analyses). Presentation of the ITT results would be more consistent with the existing labeling for products already approved for this indication (e.g., enoxaparin sodium, dalteparin sodium, fondaparinux sodium). The text and table should make clear what patients (if any were excluded from the analyses).

- In the **PRECAUTIONS** section, **Antibodies/Re-exposure** subsection: This paragraph should be revised to delete the sentence [redacted] This sentence does not contribute valuable information to the paragraph. It is somewhat vague and could be unduly promotional.
- In the **PRECAUTIONS** section, **Drug Interactions** subsection: In the original NDA submission, the sponsor proposed two paragraphs providing instructions on for switching patients from oral anticoagulants to desirudin or from desirudin to oral anticoagulants. In the approvable letter the sponsor was instructed to revise the subsection to reflect what is known. Additional guidance was requested for switching from desirudin to oral anticoagulants. The sponsor has revised the wording in this section and cites drug interaction study RH/E35 in support of the wording. RH/E35 was an open-label, non-randomized, single-center, two treatment period study [warfarin alone [10mg PO for 3 days], then PK/PD checked, followed by a 15 day washout period, and then a single dose of desirudin immediately followed by desirudin 0.3mg/kg SC bid for 3 days + warfarin 10 mg daily PO] in 12 healthy volunteers. Warfarin did not significantly affect the pharmacokinetics of desirudin; however, there was an additive effect of desirudin on aPTT and PT (INR) when desirudin and warfarin were co-administered. In this study 8 patients experienced purpura (see A. Farrell, Medical Officer's Review, p. 84).

  The sponsor's revised wording regarding switching patients from oral anticoagulants to desirudin includes information about the design and results of the drug interaction study and followed by the recommendation that:

  > "If a patient is switched from oral anticoagulants to Iprivask therapy, the oral anticoagulant activity should continue to be closely monitored with appropriate methods. That activity should be taken into account in the evaluation of the overall coagulation status of the patient during the switch to Iprivask."

  Comment: It should be noted that in the pivotal clinical trials patients were excluded from study participation if they had received oral anticoagulants within 7 days prior to start of surgery and the prophylaxis period. There appears to be no specific, documented, prospectively planned examination of converting patients from oral anticoagulant to desirudin. Nevertheless, the proposed recommendation is general, reasonable and acceptable following the results of the warfarin+desirudin drug interaction study.

  To address switching from desirudin to oral anticoagulants the sponsor proposes the following recommendation:

  [redacted]

Comment: For the pivotal clinical trials, the protocol instructions for premature discontinuation from the trial during the prophylaxis period stated that in the case of a confirmed thromboembolic event, "the trial medication must be stopped" and "Appropriate clinical action must be taken by the investigator i.e. appropriate treatment and/or prophylaxis given according to the standard practice of the hospital." There appears to be no specific, documented, prospectively planned experience with switching patients from desirudin to oral anticoagulants. The safety data from the clinical trials did not appear to indicate a problem with excessive bleeding in patients who suffered thromboembolic events and therefore, we assume, had continued anticoagulation after discontinuation from the study, so probably those general instructions were adequate. The very specific instructions that the sponsor proposes are not unreasonable. However, the very specific target numbers and timing given in the recommendation suggest that there has been specific clinical testing of this instruction. The sponsor should be requested to provide a more general recommendation for switching patients from Iprivask to oral anticoagulant or provide additional clinical support or explanation for the specific recommendation given.

IV. Additional Requests: Additional requests mentioned in the approvable letter but not indicated as required for approval were the following:

Clinical Pharmacology and Biopharmaceutics: To allow discrimination between desirudin and its metabolites, attempt to develop a specific assay method, such as [redacted] to analyze the plasma and urine samples from any future pharmacokinetic studies and revise the package insert accordingly.

Comment: The sponsor did not submit any additional information to address this request but added the following to the **CLINICAL PHARMACOLOGY** section, **Pharmacokinetic Properties, Absorption** subsection: "Pharmacokinetic parameters were calculated based on plasma concentration data obtained by a non-specific ELISA method that does not discriminate between native desirudin and its metabolites. It is not known if the metabolites are pharmacologically active." FDA Clinical Pharmacology and Biopharmaceutics review (T.-M. Chen, 2/12/03) found the response acceptable, except that the added sentences should immediately follow the **Pharmacokinetic Properties** heading and not be within the **Absorption** subsection.

Clinical: Provide safety information from the first market date of desirudin (Malaysia-11/95) to the start of the Safety Update (5/1/99); provide clinical information to support the labeling recommendations for switching from desirudin to other anticoagulants and from other anticoagulants to desirudin.

Comment: This information was submitted and included and reviewed along with the safety update.

The approvable letter also indicated that information provided in the NDA did not address use of desirudin [redacted] provide safety information and optimal dosing regimen in hepatically impaired patients and [redacted]

Comment: Clinical review concluded that there is no reason to expect that efficacy or safety of desirudin should differ among races. Therefore, no further specific investigation of the drug in other racial groups is needed. The information about race of patients in the clinical trials has been included in the description of the studies under **CLINICAL TRIALS** in the labeling.

For patients with hepatic impairment, additional information is needed. The drug is predominantly cleared by the kidney; however, patients with hepatic-impairment often have lower levels of Vitamin K-dependent coagulation factors and may respond differently to desirudin than patients with normal hepatic function. Patients with moderate or worse hepatic function were excluded from the clinical trials. Agreement to a request for a post-marketing commitment to conduct a clinical study in hepatically impaired patients to provide safety information and an appropriate dosing regimen for these patients was received from the sponsor on March 17, 2003. Regarding hepatic insufficiency, the current draft labeling states the following:

- Under **CLINICAL PHARMACOLOGY, Special Populations:** *Hepatic Insufficiency:* "No pharmacokinetic studies have been conducted to investigate the effects of Iprivask in hepatic insufficiency (see **PRECAUTIONS,** *Hepatic Insufficiency/Liver Injury* and **DOSAGE and ADMINISTRATION).**
- Under **PRECAUTIONS, Hepatic Insufficiency/Liver Injury:** "No information is available about the use of desirudin in patients with hepatic insufficiency/liver injury. Although Iprivask is not significantly metabolized by the liver, hepatic impairment or serious liver injury (*e.g.*, liver cirrhosis) may alter the anticoagulant effect of Iprivask due to coagulation defects secondary to reduced generation of vitamin K-dependent coagulation factors. Iprivask should be used with caution in these patients."
- Under **DOSAGE AND ADMINISTRATION,** *Use in Hepatic Insufficiency.* "In the absence of clinical studies in this population, dosing recommendations cannot be made at this time (see **CLINICAL PHARMACOLOGY, Metabolism, Special Populations,** *Hepatic Insufficiency,* and **PRECAUTIONS, Hepatic Insufficiency).**"

Conclusions and Recommendations:
In conclusion, the sponsor has adequately addressed all the approvability issues for Iprivask (desirudin) for the indication prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism, in patients undergoing elective hip replacement surgery. Iprivask is recommended for approval for that indication with a post-marketing agreement for study of the drug in hepatically impaired patients and pending successful negotiation of the wording of the labeling.

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

/s/

Kathy Robie-Suh
3/31/03 03:44:02 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

Kacuba, Alice

From: Mary.Elicone@aventis.com
Sent: Tuesday, April 01, 2003 2:16 PM
To: KACUBAA@cder.fda.gov
Subject: NDA 21-271 Iprivask (electronic copy of labeling being faxed as a submission today)

Dear Alice,

As agreed during yesterday's teleconference, attached are electronic copies of the Iprivask final labeling being submitted as an NDA amendment today (fax). We will also send a paper copy of the submission.

Annotated Package Insert ✓

Package Insert (Clean running text) ✓

Carton Labels (2-ct and 10-ct) ✓ ✓

Vial Labels (desirudin and diluent) ✓ ✓

NDA 21.271

LD = 4-1-03

SD = 4-1-03

Mary Elicone
Global Regulatory Coordinator

Tel: 908-304-6253
Cell: 908-392-6253
Fax: 908-304-6560
Administrative assistant: Rebecca Grenke x3071

(R)

Number of Pages Redacted 32

❖❖❖

Draft Labeling
(not releasable

Fax RC:
a.s. sheet
NDA

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation III

FACSIMILE TRANSMITTAL SHEET

/S/

DATE: March 8, 2003

To: Mary E. Elicone, RPh Global Regulatory Coordinator	**From:** Alice Kacuba, R.N., MSN, RAC
Company: Aventis Pharmaceuticals, Inc.	Division of Gastrointestinal and Coagulation Drug Products
Fax number: 908-231-3734	**Fax number:** 301-443-9285
Phone number: 908-304-6253	**Phone number:** (301) 827-1602 or 7310

Subject: NDA 21-271

Total no. of pages including cover: 3

Comments: Attached is a communication regarding NDA 21-271.

We would like to inform you that an expiratory dating period of 24 months for the drug substance stored at -20° C will be granted instead of a retest period.

Please note that the review process has not been completed yet, so at this time, we can not make any statement on the action for this review cycle for this application.

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/

Alice Kacuba
3/8/03 03:42:40 PM
CSO

APPEARS THIS WAY
ON ORIGINAL

DUPLICATE

Aventis Pharmaceuticals

Aventis

N 000BL
ORIG AMENDMENT

March 06, 2003

Ms. Alice Kacuba
Regulatory Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Center for Drug Evaluation and Research (HFD-180)
Food and Drug Administration
Document Control Room 6B-24
5600 Fishers Lane
Rockville, MD 20857

NDA 21-271
Iprivask™ (desirudin) Injection
Other: Response to FDA Request

Dear Ms. Kacuba:

Reference is made to NDA 21-271 Iprivask™ (desirudin) Injection and the Approvable Letter for NDA 21-271 dated May 14, 2001. Reference is also made to the December 27, 2002 submission that included PDF versions of the labeling.

Attached are enlarged paper copies of the carton and vial labeling, as requested.

If you should have any questions or comments, please contact the undersigned by phone (908-304-6253) or by fax (908-231-3734).

Sincerely,

Mary E. Elicone, RPh
Global Regulatory Coordinator
Attachments

Aventis Pharmaceuticals Inc. · www.aventis.com
200 Crossing Boulevard · PO Box 6890 · Bridgewater, NJ 08807-0890 · Telephone (908) 304-7000

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0338
Expiration Date: March 31, 2003
See OMB Statement on page 2.

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
Aventis Pharmaceuticals Inc.	3/06/2003
TELEPHONE NO. (Include Area Code)	**FACSIMILE (FAX) Number *(Include Area Code)***
(908) 304-7000	(908) 231-3734
APPLICANT ADDRESS (Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):	**AUTHORIZED U.S. AGENT NAME & ADDRESS (Number, Street, City, State, ZIP Code, telephone & FAX number) IF APPLICABLE**
200 Crossing Blvd. Bridgewater, N.J. 08807-0890	

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued): NDA 21-271

ESTABLISHED NAME (*e.g., Proper name, USP/USAN name*)	PROPRIETARY NAME (*trade name*) IF ANY
desirudin	Iprivask™

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME (*If any*)	CODE NAME (*If any*)
n/a	RPR205511/CGP39393

DOSAGE FORM:	STRENGTHS:	ROUTE OF ADMINISTRATION:
Single dose (15 mg) lyophilized powder	15 mg	Subcutaneous injection

(PROPOSED) INDICATION(S) FOR USE:
Iprivask™ is indicated for the prevention of deep vein thrombosis, which may lead to pulmonary embolism, in patients undergoing elective hip replacement surgery.

APPLICATION INFORMATION

APPLICATION TYPE (check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug — Holder of Approved Application

TYPE OF SUBMISSION (check one) ☐ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY, MANUFACTURING AND CONTROLS SUPPLEMENT ☒ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION: _____

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION
Response to FDA Request

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED N/A

THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

see NDA 21-271 submitted on June 28, 2000

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

see NDA 21-271 submitted on June 28, 2000

This application contains the following items: *(Check all that apply)*	
☐	1. Index
☒	2. Labeling (check one) ☐ Draft Labeling ☐ Final Printed Labeling
☐	3. Summary (21 CFR 314.50 (c))
☐	4. Chemistry section
☐	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50 (d)(1), 21 CFR 601.2)
☐	B. Samples (21 CFR 314.50 (e)(1), 21 CFR 601.2 (a)) (Submit only upon FDA's request)
☐	C. Methods validation package (e.g., 21 CFR 314.50 (e)(2)(i), 21 CFR 601.2)
☐	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50 (d)(2), 21 CFR 60[illegible].2)
☐	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50 (d)(3), 21 CFR 601.2)
☐	7. Clinical Microbiology (e.g., 21 CFR 314.50 (d)(4))
☐	8. Clinical data section (e.g., 314.50 (d)(5), 21 CFR 601.2)
☐	9. Safety update report (e.g., 21 CFR 314.50 (d)(5)(vi)(b), 21 CFR 601.2)
☐	10. Statistical section (e.g., 21 CFR 314.50 (d)(6), 21 CFR 601.2)
☐	11. Case report tabulations (e.g., 21 CFR 314.50 (f)(1), 21 CFR 601.2)
☐	12. Case reports forms (e.g., 21 CFR 314.50 (f)(2), 21 CFR 601.2)
☐	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
☐	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355(b)(2) or (j)(2)(A))
☐	15. Establishment description (21 CFR Part 600, if applicable)
☐	16. Debarment certification (FD&C Act 306 (k)(1))
☐	17. Field copy certification (21 CFR 314.50 (k)(3))
☐	18. User Fee Cover Sheet (Form FDA 3397)
☐	19. Financial Information (21 CFR Part 54)
☒	20. OTHER *(Specify)* Paper Copies of enlarged vial and carton labels

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660 and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
[signature]	Mary E. Elicone, RPh Global Regulatory Coordinator (Aventis)	3/06/2003

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
200 Crossing Boulevard Mailstop: BX2-206-B Bridgewater, NJ 08807-0890	(908) 304-6253

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
BER, HFM-99
401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Dr., Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it desplays a currently valid OMB control number.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO (Division/Office):
Associate Director, Medication Error Prevention
Office of Drug Safety, HFD-400
(Rm. 15B-03, PKLN Bldg.)

FROM: Alice Kacuba, Regulatory Health Project Manager, HFD-180

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
February 25, 2003		21-271	Complete response to AE letter	October 3, 2002

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Iprivask (desirudin) Injection [redacted]	Class 2 resubmission	Anti-thrombin	March 5, 2003

NAME OF FIRM: Aventis

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE--NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☒ OTHER *(SPECIFY BELOW)*: Trade name review

COMMENTS, CONCERNS, and/or SPECIAL INSTRUCTIONS: We will most likely be taking an AP action on this application this review cycle. Your earlier review found the proposed tradename of Iprivask acceptable but asked that prior tc approval, we consult you again on tradename. Please advise if the proposed tradename of Iprivask remains acceptable.

There will be no hardcopy of this consult.

Thank you for your assistance in this matter.

PDUFA DATE: April 3, 2003 (Divisional due date for all discipline reviews to be completed is Feb 27, 2003)
ATTACHMENTS: Draft Package Insert, Container and Carton Labels
CC:
Archival NDA 21-271
HFD-180/Division File
HFD-180/Kacuba
HFD-180/Marie Kowblanky, Liang Zhou

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Alice Kacuba
2/25/03 05:03:15 PM

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ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Dr. Peter Cooney, HFD-805, Room 18B-09	FROM: Division of GI and Coagulation Drug Products (HFD-180)/ Alice Kacuba (301) 827-1602

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
Feb 25, 2003		21-271	Resubmission (2nd cycle) of original NDA	October 3, 2002

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Iprivask ([redacted] [redacted]	Class 2 resubmission	Anticoagulant	March 12, 2003

NAME OF FIRM: Aventis

REASON FOR REQUEST

I. GENERAL

NEW PROTOCOL
☐ PROGRESS REPORT
☐ NEW CORRESPONDENCE
☐ DRUG ADVERTISING
☐ ADVERSE REACTION REPORT
☐ MANUFACTURING CHANGE/ADDITION
☐ MEETING PLANNED BY
☐ PRE-NDA MEETING
☐ END OF PHASE II MEETING
☐ RESUBMISSION
☐ SAFETY/EFFICACY
☐ PAPER NDA
☐ CONTROL SUPPLEMENT
☐ RESPONSE TO DEFICIENCY LETTER
☐ FINAL PRINTED LABELING
☐ LABELING REVISION
☐ ORIGINAL NEW CORRESPONDENCE
☐ FORMULATIVE REVIEW
☐ OTHER *(SPECIFY BELOW)*:

COMMENTS/SPECIAL INSTRUCTIONS:

2nd sending of the consult request for micro review.

Background: The purpose of this consult request is to obtain a micro review of the resubmission to NDA 21-271. Aventis has submitted a complete response to the May 14, 2001 AE letter for this NDA. CMC has requested a consult be sent to you. Microbiology completed a review of the original NDA.

The hard copy of this consult contains the microbiology section of the resubmission, the past AE letter and cmc Discipline Review letter.

This consult was originally set on Dec 4, 2002. According to your Feb 25, 2003 email response to my email inquiry dated Feb 24, 2003, you indicate that our consult request was never received by you.

The user fee goal date is April 4, 2003 and the Division goal date is February 27, 2003. Please complete your review by March 5, 2003. Please contact Liang Zhou, cmc team leader for HFD-180, by Thursday, Feb 27, 2003 if you have concerns over this request.

The cmc reviewer for this NDA is Marie Kowblansky. She can be reached at 7-7466.
I can be reached at 7-1602.

Thank you in advance for your review.

cc:
Archival NDA 21-271
HFD-180/Division File
HFD-180/Kacuba
HFD-180/Marie Kowblanky, Liang Zhou

SIGNATURE OF REQUESTER	METHOD OF DELIVERY (Check one) ☐ MAIL ☐ HAND

SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Alice Kacuba
2/25/03 02:47:19 PM

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DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Clinical Pharmacology & Biopharmaceutics (HFD 870)** **Tracking/Action Sheet for Formal/ Informal Consults**

From: Tien-Mien Chen, Ph.D. (HFD-870)			**To: DOCUMENT ROOM (LOG-IN and LOG-OUT) Please log-in this consult and review action for the specified IND/NDA submission**	
DATE: 02/11/03	IND No.: Serial No.:	NDA No. 21-271 Serial No.: N-000 BZ	DATE OF DOCUMENT **10/03/02**	
NAME OF DRUG **[Iprivask (Desirudin) Injection]**	PRIORITY CONSIDERATION		Date of informal/Formal Consult: 10/09/02	

NAME OF THE SPONSOR: **[Aventis Pharmaceuticals]**

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ BIOAVAILABILITY STUDIES	☒ LABELING REVISION
☐ IN-VITRO METABOLISM	☐ IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☐ PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POPPK ISSUES	☐ MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)	☐ OTHER *(SPECIFY BELOW)*: [ ]
☐ PHASE IV RELATED		

REVIEW ACTION

☐ NAI (No action indicated)	☐ Oral communication with	☐ Formal Review/Memo (attached)
☐ E-mail comments to:	Name: [ ]	☒ See comments below
☐ Medical ☐ Chemist ☐ Pharm-Tox	☐ Comments communicated in	☐ See submission cover letter
☐ Micro ☐ Pharmacometrics ☐ Others	meeting/Telecon. see meeting minutes	☐ OTHER *(SPECIFY BELOW)*:
(Check as appropriate and attach e-mail)	dated: [ ]	[ ]

REVIEW COMMENT(S)

☒ **NEED TO BE COMMUNICATED TO THE SPONSOR** ☐ **HAVE BEEN COMMUNICATED TO THE SPONSOR**

COMMENTS/SPECIAL INSTRUCTIONS:

[X] Iprivask (desirudin) Injection (NDA 21-271) received an "Approvable Letter" on 05/14/01. In the current submission dated 10/03/02, electronic copies of proposed draft labeling and responses to the Agency's comments were submitted for review.

OCPB's comment in the Approvable Letter (on page 4 under "Although not required for approval, we request you provide the foll owing at your earliest convenience:") states:

Clinical Pharmacology and Biopharmaceutics:

Calculated pharmacokinetic parameters were based on plasma concentration data obtained from a non-specific ELISA method that does not discriminate between native desirudin and its metabolites. Attempt to develop a specific assay method, such as an —— assay to analyze the plasma and urine samples from any future pharmacokinetics studies and revise your package insert accordingly.

Aventis' Response:

this time, no pharmacokinetics studies are planned and only a non-specific ELISA method is currently available to provide plasma concentrations data for desirudin and its metabolites. The two statements,

" Pharmacokinetic parameters were calculated based on plasma concentration data obtained by a non-specific ELISA method that does not discriminate between native desirudin and its metabolites. It is not known if the metabolites are pharmacologically active.",

have been added to the Pharmacokinetics properties, absorption" section on drug labeling.

Recommendation:

Aventis' response to the above OCPB comment and proposed labeling revisions submitted are acceptable from OCPB viewpoint. How ever, the sponsors proposed statements (shown above in Aventis' response) should precede absorption subsection and not within. Please see Appendix 1 for further details and OCPB's labeling comment should be conveyed to the sponsor. Appendix 2 contains sponsor's u nannotated proposed labeling for completion.

SIGNATURE OF REVIEWER: Tien-Mien Chen, Ph.D.	Date 02/11/03
SIGNATURE OF TEAM LEADER: Suresh Doddapaneni, Ph.D.	Date 02/12/03
CC.: HFD # [180]; TL: [SD]	**Project Manager:** A. Kacuba **Date** 02/12/03

ıchments:

Appendix 1- Clinical Pharmacology and Biopharmaceutics related sections of the package insert with OCPB's revisions to the sponsor's proposals.

Appendix 2- Sponsor's proposed package insert

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/s/

Tien-Mien Chen
2/12/03 10:55:40 AM
BIOPHARMACEUTICS

Suresh Doddapaneni
2/12/03 11:07:14 AM
BIOPHARMACEUTICS