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#21

Division of Medication Errors and Technical Support
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

Label and Labeling Review

DATE OF REVIEW: February 5, 2003

NDA: 21-271

NAME OF DRUG: **Iprivask**
(Desirudin for Injection)
15 mg

NDA HOLDER: Aventis Pharmaceutical Products, Inc.

I. INTRODUCTION

This consult is in response to a December 10, 2002 request by the Division of Gastrointestinal and Coagulation Drug Products to review the container labels, carton and package insert labeling for possible interventions in minimizing medication errors. DMETS completed a Proprietary Name Review for "Iprivask" in December 5, 2002 and had no objection to the use of the proposed proprietary name (see ODS 00-0208-1).

PRODUCT INFORMATION

Iprivask contains the active ingredient, desirudin, and is indicated for the prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism, in patients undergoing hip replacement surgery. The recommended dose is 15 mg every 12 hours administered by subcutaneous injection. Iprivask is supplied as 2 vials of 15 mg desirudin with 2 ampules of 0.6 mL Mannitol (3% w/v) in Water for Injection and 10 vials of 15 mg desirudin with 10 ampules of 0.6 mL of Mannitol (3% w/v) in Water for Injection.

II. LABELING, PACKAGING AND SAFETY RELATED COMMENTS

DMETS has reviewed the container labels, carton and insert labeling of Iprivask and has identified several areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENT

1. According to an e-mail, dated January 27, 2003 to DMETS, from the chemist, the product is manufactured to contain a 5% overfill of the lyophilized drug product in the vial (i.e., 15.75 mg desirudin). However, we note that the product is labeled 15 mg. The strength should be revised to read 15.75 mg/vial on all labels and labeling.

2. Based on the above information, we calculate that once reconstituted with 0.5 mL of diluent, one would have to withdraw 0.48 mL of the reconstituted solution to achieve a 15 mg dose (see below).

   $\frac{15.75\ mg}{0.5\ mL} = \frac{15\ mg}{X\ mL}$

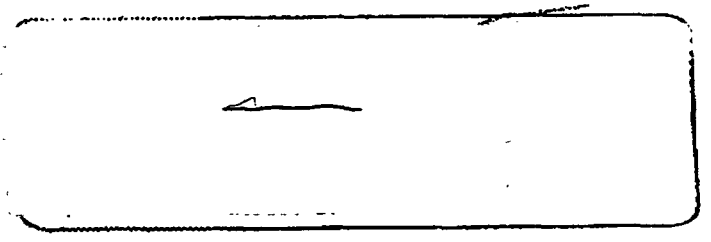
   X mL=0.48 mL

   In addition, we calculate that one must use 0.525 mL of diluent to have a resulting concentration of 15 mg/0.5 mL (see below). Please comment.

   $\frac{15\ mg}{0.5\ mL} = \frac{15.75\ mg}{X\ mL}$

   X mL=0.525 mL

B. CONTAINER LABEL (Iprivask)



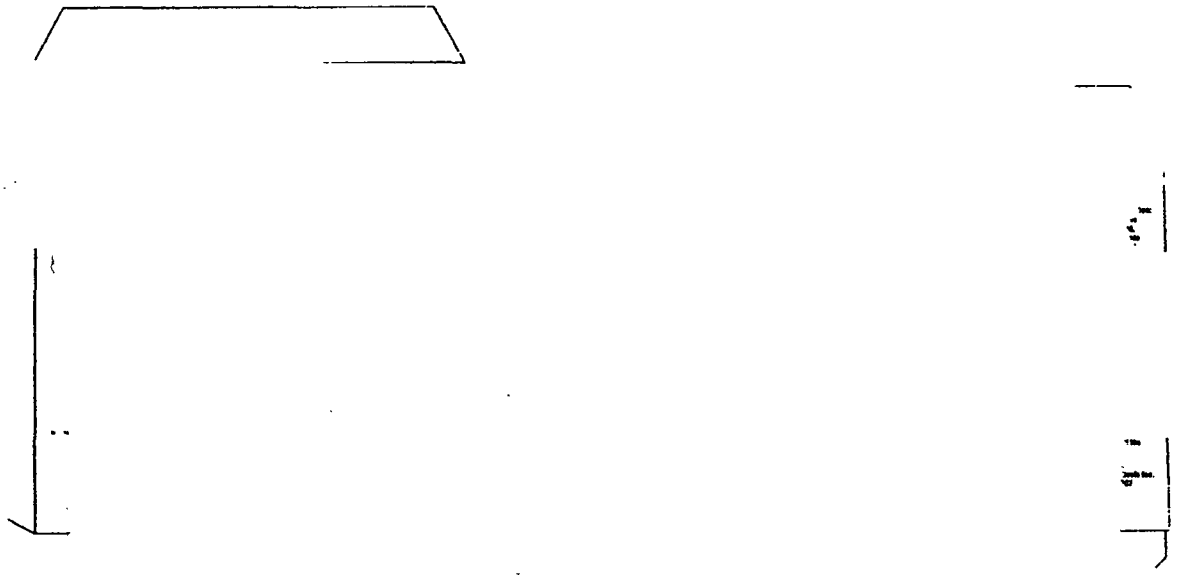
1. See General Comment.

2. In order to increase the prominence of the established name, we recommend changing the established name ——————— to "Desirudin for Injection."

3. Revise the strength to read 15.75 mg/vial.

4. If space permits, include a statement that the vial should only be reconstituted with the diluent provided (3% Mannitol in Water For Injection). Additionally, include a statement that details how many "mg" of Iprivask will be contained in each "mL" once reconstituted with 0.5 mL of diluent. For example, "Once reconstituted with 0.5 mL of Mannitol Injection 3%, each 0.5 mL contains XX mg of Iprivask.

C. CARTON LABELING (2's and 10's)



1. See General Comment.

2. See comments under B2.

3. We recommend relocating the statement "Single dose vials. Discard unused portion" to the front of the label to increase its prominence.

4. We recommend revising the statement [redacted] to "Usual Dosage: 15 mg subcutaneously every 12 hours" to minimize potential errors with the use of this product.

5. Increase the prominence of the directions for reconstitution. The statement may need to be relocated to the back panel to provide sufficient space.

D. INSERT LABELING

1. See General Comment.

2. DESCRIPTION

   See General Comments under section A

3. Throughout the package insert, the route of administration, subcutaneous injection, is abbreviated as "SC". We recommend changing the abbreviation "SC" to read "subcutaneous" in order minimize user errors.

4. DOSAGE AND ADMINISTRATION

   The table for "Use in Renal Insufficiency" does not contain the route of administration. We recommend revising the dosing instruction to include the route of administration. For example, "5 mg every 12 hours by subcutaneous injection".

5. Administration-Direction for Preparation

   a. Revise step 2 to read as follows: Reconstitute each vial with XX mL of provided diluent (3% Mannitol in Water For Injection). Once reconstituted, each XX mL contains XX mg of desirudin.

   b. Revise step 5 to read as follows: ...when stored at room temperature...(note insert "at").

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III. RECOMMENDATIONS

DMETS recommends the implementation of the proposed labeling in conjunction with the labeling revisions outlined above in order to prevent the potential for medication errors.

DMETS would appreciate feedback of the final outcome of this consult. We are willing to meet with the Division for further discussion as well. If you have any questions concerning this review, please contact Sammie Beam, project manager, at 301-827-3242.

Hye-Joo Kim, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support

Concur:

Alina Mahmud, RPh
Team Leader
Division of Medication Errors and Technical Support

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/s/

Hye-Joo Kim
2/21/03 03:28:55 PM
PHARMACIST

Carol Holquist
2/21/03 03:30:22 PM
PHARMACIST

Jerry Phillips
2/21/03 04:20:51 PM
DIRECTOR

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*:
Director, Division of Medication Errors and Technical Support (DMETS), HFD-420
PKLN Rm. 6-34

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

DATE	IND NO.	NDA NO.	TYPE OF DOCUMENT	DATE OF DOCUMENT
12-5-02		21-271	NDA resubmission	Oct 3, 2002

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Iprivask		Anti-thrombin	Feb 20, 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: **Your consult review requested we send the vial and cartons labels to you for review. Attached to the hardcopy consult are the draft vial and carton labels.**

DUFA DATE: **April 3, 2003 (Divisional goal date for all reviews to be completed is Feb 27, 2003).**
ATTACHMENTS: Draft Package Insert, Container and Carton Labels

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

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/s/

Alice Kacuba
12/5/02 09:41:28 AM

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CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: 12/10/02	**DUE DATE:** 02/10/03	**ODS CONSULT #:** 00-0208-2

TO: Robert Justice, M.D.
Director, Division of Gastrointestinal and Coagulation Drug Products
HFD-180

THROUGH: Alice Kacuba
Project Manager
HFD-180

PRODUCT NAME:	**SPONSOR:**
Iprivask (Desirudin for Injection) 15 mg **NDA #: 21-271**	Aventis Pharmaceutical Products, Inc.

SAFETY EVALUATOR: Hye-Joo Kim, Pharm.D.

SUMMARY: In response to a consult from the Division of Gastrointestinal and Coagulation Drug Products (HFD-180), the Division of Medication Errors and Technical Support (DMETS) reviewed the proposed container labels, carton and package insert labeling of Iprivask for possible interventions that may help minimize medication errors.

DMETS RECOMMENDATION: DMETS recommends the implementation of the label revisions outlined in section II of this review in order to minimize the potential for medication errors.

Carol Holquist, R.Ph.
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

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

FACSIMILE TRANSMITTAL SHEET

DATE: December 5, 2002

To: Huy Q. Turong, MS Assistant Director	**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: 908-231-2786	**Phone number:** (301) 827-1602 or 7310

/S/

Subject: NDA 21-271 Information Request

Total no. of pages including cover: 3

Comments: Attached is an Information Request. Please respond, as soon as possible, as an amendment to the NDA. Thank you.

Document to be mailed: ☐ YES ☑ NO

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.

If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 827-1602. Thank you.

In addition, I would like to request 2 desk copies of Volume 1.1. Thank you.

/S/

We would like to request the following information:

1. Please provide additional information regarding the 1st and 2rd WHO International Thrombin Reference Standards which were used in your bioassays. Provide copies of WHO Certificates of Analysis for the two standards, as well as the results of any other characterization measurements that you may have conducted.

2. Provide the date when you started using the 2nd thrombin standard and ceased using the 1st.

3. Provide a description and results of all experiments that support your conclusion that the activity of the two standards differs [redacted]. Include comparative bioassay results for all samples that were measured against both thrombin standards.

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/s/

Alice Kacuba
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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
Dec 4, 2002		21-271	Resubmission (2nd cycle) of original NDA	October 3, 2002

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Iprivask : [redacted]	Class 2 resubmission	Anticoagulant	February 16, 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:

Background: 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 user fee goal date is April 4, 2003 and the Division goal date is February 27, 2003. Please complete your review by Feb 16, 2003.

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.

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

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SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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/s/

Alice Kacuba
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CONSULTATION RESPONSE
DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: 10/28/02	**DUE DATE:** 12/12/02	**ODS CONSULT #:** 00-0208-1

TO:

Robert Justice, M.D.
Director, Division of Gastrointestinal and Coagulation Drug Products
(HFD-180)

THROUGH:

Alice Kacuba
Project Manager
(HFD-180)

PRODUCT NAME: **Iprivask** (Desirudin for Injection) 15 mg **NDA#: 21-271**	**NDA SPONSOR:** Aventis Pharmaceutical Products, Inc.

SAFETY EVALUATOR: Charlie Hoppes, RPh, MPH

SUMMARY:
In response to a consult from the Division of Gastrointestinal and Coagulation Drug Products (HFD-180), the Medication Errors and Technical Support (DMETS) conducted a review of the proposed proprietary name "Iprivask" to determine the potential for confusion with approved proprietary and established names as well as pending names.

DMETS RECOMMENDATION:
DMETS has no objections to the use of the proprietary name, Iprivask. This is considered a tentative decision and the firm should be notified that the name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from the signature date of this document. Please provide container labels and carton labeling for safety evaluation upon receipt.

NOTE: This review contains proprietary and confidential information that should not be released to the public.

Carol Holquist, R.Ph.
Deputy Director,
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: November 12, 2002

NDA# 21-271

NAME OF DRUG: Iprivask (Desirudin for Injection) 15 mg

NDA HOLDER: Aventis Pharmaceutical Products, Inc.

*****NOTE: This review contains proprietary and confidential information that should not be released to the public.*****

I. INTRODUCTION:

This consult is written in response to a request from the Division of Gastrointestinal and Coagulation Drug Products (HFD-180), for an assessment of the proposed proprietary name Iprivask. On October 18, 2000, DMETS reviewed the proprietary name ' for this drug product and Draft package insert labeling, was reviewed for possible interventions in minimizing medication errors.

PRODUCT INFORMATION

Iprivask is the proposed proprietary name for, Desirudin for Injection, which is indicated for the prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism, in patients undergoing hip replacement surgery. The recommended dose of Iprivask is 15 mg every 12 hours administered by subcutaneous injection. Iprivask is supplied as 2 vials of 15 mg desirudin with 2 ampules of 0.5 mL Mannitol (3% w/v) in Water for Injection and 10 vials of 15 mg desirudin with 10 ampules of 0.5 mL of Mannitol (3% w/v) in Water for Injection.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to Iprivask to a degree where potential confusion between drug names could occur under

[1] MICROMEDEX Healthcare Intranet Series, 2000, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes the following published texts: DrugDex, Poisindex, Martindale (Parfitt K (Ed), Martindale: The Complete Drug Reference. London: Pharmaceutical Press. Electronic version.), Index Nominum, and PDR/Physician's Desk Reference (Medical Economics Company Inc, 2000).
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[3] The Established Evaluation System [EES], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 00-02, and the electronic online version of the FDA Orange Book.

the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[4]. The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies for each name, consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Iprivask. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel identified one established name that was thought to have the potential for confusion with Iprivask. This product is listed in Table 1 (see below), along with the dosage form available and usual dosage.

2. DDMAC did not have concerns about the name with regard to promotional claims.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Established name, Dosage form(s)	Usual adult dose*	Other**
Iprivask	Desirudin for Injection,	15 mg every 12 hours administered by subcutaneous injection	
Diprivan	Propofol Injectable Emulsion, 10 mg/mL	Start infusion rate at 5 mcg/kg/min and increase until the proper level of sedation is achieved.	LA

*Frequently used, not all-inclusive.
**L/A (look-alike)/S/A (sound-alike)
***not marketed, not approved

B. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within FDA for the proposed proprietary name to determine the degree of confusion of Iprivask with other U.S. drug names due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 106 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process.

[4] WWW location http://www.uspto.gov/tmdb/index.html.
[5] Data provided by Thomson & Thomson's SAEGIS(tm) Online Service, available at www thomson-thomson.com.

An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Iprivask (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

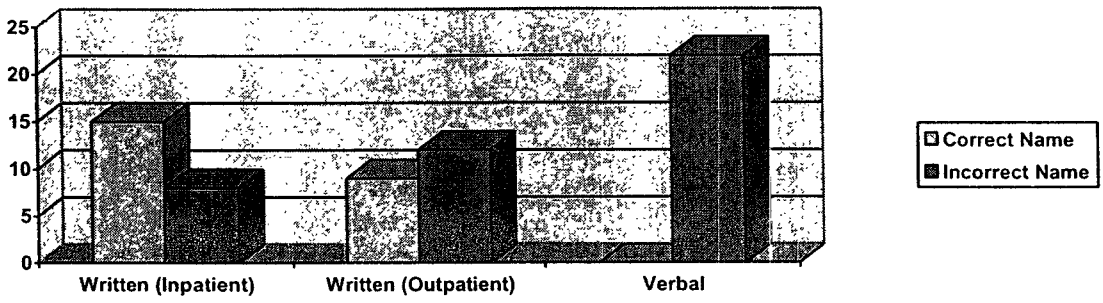
HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: Iprivask 15mg Sig: 15mg SQ q12°x 3 more days	Iprivask 15 mg Sub-Q every 12 hours for 3 days.
Inpatient RX: Iprivask 15mg SQ x 1 Discharge meds	

2. Results:

The results for Iprivask are summarized in Table I.

Table I

Study	# of Participants	# of Responses (%)	Correctly Interpreted (%) Iprivask	Incorrectly Interpreted (%)
Written Inpatient	39	23 (59%)	15 (65%)	8 (35%)
Written Outpatient	35	21 (60%)	9 (43%)	12 (57%)
Verbal	32	22 (69%)	0 (0%)	22 (100%)
Total	106	66 (62%)	24 (36%)	42 (64%)



Among participants in the written prescription studies, 20 of 44 respondents (45%) interpreted the name incorrectly. The interpretations were misspelled variations of "Iprivask". Incorrect interpretations of written prescriptions included: *Ipravask, Iprivase, Ipuvask, Ipnovel, Ipravaar, Ipriva, Ipmivask, Ipsivask* (3 occurrences), *Iprivack* (2 occurrences), *Iprivash* (2 occurrences), *Ipivask* (2 occurrences), *Ipiwask, Iprivax, Ipsivash,* and *Ipsivisk.* None of the interpretations are similar to a currently marketed drug product.

Among participants in the verbal prescription studies, 22 of 22 (100%) interpreted the name incorrectly. Most incorrect name interpretations were phonetic variations of "Iprivask". Incorrect interpretations of the verbal prescription included: *Iprivasc* (6 occurrences), *Iprovask, Iprovasc* (8 occurrences), *Ipravasç* (3 occurrences), *Improfast, Ipravax, Iprivax,* and *Epivas.* None of the interpretations are similar to a currently marketed drug product.

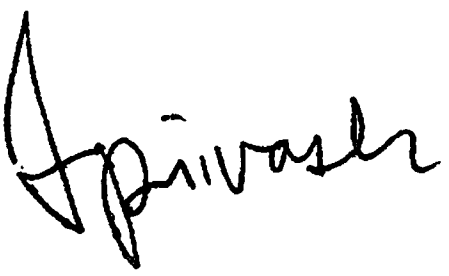
C. SAFETY EVALUATOR RISK ASSESSMENT

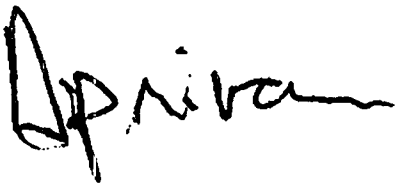
*****NOTE: This review contains proprietary and confidential information that should not be released to the public.*****

In reviewing the proposed proprietary name "Iprivask", the primary concerns raised related to look-alike, sound-alike confusion with a name already in the U.S. marketplace and a name under FDA review. The products considered to have potential for name confusion with **Iprivask** were Diprivan and [redacted]

DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that Iprivask can be confused with Diprivan or [redacted] The majority of interpretations from the written and verbal prescription studies were phonetic/ misspelled interpretations of the drug name Iprivask. None of the interpretations are similar to a currently marketed drug product.

Diprivan Injectable Emulsion is the proprietary name for Propofol Injectable Emulsion. Diprivan is indicated for both induction and/or maintenance of anesthesia as part of a balanced anesthetic technique for inpatient and outpatient surgery and also for monitored anesthesia care (MAC) sedation during diagnostic procedures. Dosing for sedation begins with an infusion rate of 5 mcg/kg/min, which may be increased until the proper level of sedation is achieved. Diprivan Injectable Emulsion is available in ready to use 20 mL, 50 mL, and 100 mL infusion vials and 50 mL pre-filled syringes containing 10 mg/mL of propofol. *Diprivan* and *Iprivask* may look similar when written (see writing sample on page 6).





The name pair shares the middle letters "priva". Secondly, a cursive "I" in Iprivask may look like the "D" in Diprivan. Finally, a cursive "k" in Iprivask may look like the "n" in Diprivan. Despite look-alike similarities, Diprivan and Iprivask have differences which make them distinct from each other. Diprivan and Iprivask have different dosage forms and routes of administration. Diprivan is an injectable emulsion for intravenous administration while Iprivask is a "for injection" dosage form which is intended for subcutaneous administration. These differences become more obvious when the volumes to be administered are compared. After Iprivask is reconstituted, 0.5 mL is to be administered, while the smallest vial of Diprivan is 20 mL (a 40-fold difference). Additionally, Diprivan is ordinarily used in a specialized setting with health care practitioners, e.g., anesthesiologists, who are skilled in its use. Although it is possible for the names to be confused, the risk of dispensing the wrong medication should be low based on the differences between the medications including route of administration, dosage forms, strengths, volumes to be administered, and usual practice setting.

[redacted] is a proposed proprietary name for Warfarin Sodium Tablets, USP. Currently, [redacted] is not approved in the United States. At the time of its evaluation in a DMETS consult dated April 26, 2002, [redacted], the name was not recommended for approval into the marketplace. However, the acceptability of the name is still pending at the Division level. Warfarin Sodium is indicated for the prophylaxis and/or treatment of venous thrombosis, pulmonary embolism, and the thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement. Warfarin Sodium is also used to reduce the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction. The dosing of Warfarin Sodium must be individualized according to a patient's sensitivity to the drug as indicated by the Prothrombin Time/International Normalized Ratio (PT/INR). It is recommended that Warfarin Sodium therapy be initiated with a dose of 2 mg to 5 mg per day with dosage increments based on the results of PT/INR ratio determinations. [redacted] and Iprivask may sound similar when spoken. Each name has three syllables. Although the first syllable of each name [redacted] ' vs. "Ip" share phonetic similarities, the last two syllables of each name " [redacted] " vs. "ivask", are virtually indistinguishable in sound. Despite sound-alike similarities, [redacted] and Iprivask have differences which make them distinct from each other. [redacted] and Iprivask have different dosage forms and routes of administration. [redacted] is a tablet for oral administration while Iprivask is a "for injection" dosage form which is intended for subcutaneous administration. In addition, [redacted] and Iprivask have different strengths 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, and 10 mg vs. 15 mg respectively, and dosing intervals, once daily vs. twice daily respectively. Although it is possible for the names to be confused, the risk of dispensing the wrong medication should be low based on the differences between the medications including route of administration, dosage forms, strengths, and dosing intervals.

III. RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name Iprivask.

2. Please provide container labels and carton labeling for safety evaluation upon receipt.

This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary and established names from this date forward.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, Project Manager, at 301-827-3242.

Charlie Hoppes, RPh, MPH
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, RPh
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-271

Aventis Pharmaceuticals Inc.
Attention: Huy Q. Truong, MS
Assistant Director
200 Crossing Boulevard
Mail Station BX2-206C
Bridgewater, NJ 08807-0890

Dear Ms. Truong:

We acknowledge receipt on October 4, 2002 of your October 3, 2002 resubmission to your new drug application for Iprivask™ (desirudin) Injection.

We consider this a complete, class 2 response to our April 16, 2001 action letter. Therefore, the user fee goal date is April 3, 2003.

If you have any question, call me at (301) 827-1602.

Sincerely,

{See appended electronic signature page}

Alice Kacuba, R.N., MSN, RAC
Regulatory Health Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Alice Kacuba
10/24/02 03:13:13 PM

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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
October 21, 2002		21-271	Complete response to AE letter	October 3, 2002

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Iprivask (desirudin) Injection	Class 2 resubmission	Anti-thrombin	Feb 20, 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 have received a complete response to the AE letter for the product formerly known as [redacted]. The firm is proposing Iprivask as the tradename.

One hardcopy of this consult will contain a copy of the package insert, carton, and vial label.

The package insert is also available in the edr under the October 3, 2002 submisison.

PDUFA DATE: April 3, 2003 (Divisional due date for all discipline reviews to be completed is March 2, 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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Alice Kacuba
10/21/02 12:07:14 PM

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

REQUEST FOR CONSULTATION

TO *(Division/Office)*: Steve Moore, Team Leader and Janice Brown, Chemistry Reviewer, HFD-510

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

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

NAME OF DRUG	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE
Iprivask (desirudin) Injection	Class 2 response	Anti-thrombin	Feb 20, 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
- XXXX OTHER *(SPECIFY BELOW)*:

COMMENTS/SPECIAL INSTRUCTIONS: 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. You completed a prioe cmc review on March 26, 2001.

The hard copy of this consult contains ~~~~ are the cmc volumes). In the hardcopy of the consult, I have in included a copy of the AE letter.

The user fee goal date is April 3, 2003 and the Division goal date is March 2, 2003. Please complete your review by Feb 20, 2003.

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.

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

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/s/

Alice Kacuba
10/21/02 11:43:15 AM
consult

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M E M O R A N D U M

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

Date: May 11, 2001

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

Subject: NDA 21-271 [redacted] (desirudin)
submitted June 28, 2000

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

Background and Rationale:
Desirudin (RPR205511; CGP39393) is a selective thrombin inhibitor developed for use in treating and preventing deep vein thrombosis. In this submission desirudin is evaluated for efficacy and safety in the prophylaxis of deep vein thrombosis (DVT) following elective total hip replacement surgery. The proposed dose is 15 mg desirudin administered twice daily by subcutaneous (sc) injection preoperatively for 9-12 days.

To support the desired indication the sponsor has submitted three adequate and well-controlled clinical trials: RH/E23, RH/E28 and RH/E25. These studies enrolled a total of 3643 patients, 2109 treated with desirudin, 498 with unfractionated heparin (UFH), and 1036 with enoxaparin. Also, a supporting open-label, dose-ranging study (RH/PT3) is submitted. Safety information is derived from the three efficacy trials plus 2 additional studies (2159 patients) for prevention of DVT. Additional studies have been done investigating desirudin for use in treatment of acute coronary syndromes; however, route of administration in those studies was intravenous except for one study (RH/E52).

The sponsor has requested a waiver for studies in pediatric patients because of inapplicability of the indication to the pediatric population.

Desirudin has been investigated under IND 34,046 initially by Novartis with the application being transferred to Rhone-Poulenc Rorer Pharmaceuticals Inc. on July 16, 1998. The drug is outlicensed to Aventis from Novartis.

Desirudin is approved for use in the European Union (July 9, 1997) for the indication of prevention of DVT in patients undergoing elective hip and knee replacement surgery.

Chemistry:
Desirudin is an rDNA derived anticoagulant identical to naturally occurring hirudin (leech anticoagulant), except that it lacks a sulfate group on Tyr-63. It is a 55 amino acid polypeptide

with a molecular weight of 6963.52. It is supplied as a sterile white powder designed for reconstitution as a solution with 3% mannitol. Reconstituted desirudin has pH of 7.4 and is stable for 24 hours at room temperature.

Toxicology and Clinical Pharmacology Information:
In acute toxicity studies in rats no significant toxicity other than bleeding, local inflammation and granulation at injection sites was seen at doses up to 332mg/kg (dose limited by solubility and volume constraints). In dogs some animals developed arteritis. Special studies demonstrated an increase in specific antibodies and IgG titer in dogs receiving 2mg/kg IV for 10 days followed by two booster injections. Studies in guinea pigs showed an increase in antibodies only when desirudin was given with Freund's adjuvant. No non-rodent subacute toxicity study has been done using subcutaneous administration of desirudin. No long-term studies in animals have been performed to evlauate the carcinogenic potential of desirudin. No genotoxic effects were seen in Ames test, Chinese hamster lung cell mutation test or rat micronucleus test; however, results in Chinese hamster ovarian cell chromosome aberration tests were equivocal. No effects were found on fertility or reproductive performance in rats. (See FDA Pharmacology Review by Y. Chopra finalized 5/4/01 and Supervisory Pharmacology Memorandum by J. Choudary finalized 5/4/01).

Desirudin subcutaneously administered to rats at about 0.3 to 4 times the recommended human dose based on body surface area and in rabbits at IV doses of about 0.3 to 3 times the recommended human dose based on body surface area showed teratogenic effects (e.g., cleft palate, omphalocele, asymetric and fused sternebrae, edema, edema, shortened hind limbs, spina bifida, hydrocephalus). Desirudin is classified as Pregnancy Category C. (See FDA Pharmacology Review by Y. Chopra finalized 5/4/01 and Supervisory Pharmacology Memorandum by J. Choudary finalized 5/4/01).

Desirudin is readily absorbed from subcutaneous tissue with a C_{max} at 1-3 hours and distributes in the extracellular space. Non-specific serum protein binding is negligible but the drug binds specifically and irreversibly to circulating thrombin. Metabolism and excretion is predominantly via the kidney (about 40-50% of dose). Rate of clearance is similar to the glomerular filtration rate. Plasma half-life is about 2 hours (after SC or IV administration). Half-life is prolonged and elimination rate slowed in moderate and severe renal failure necessitating a dose adjustment under these conditions. Clinical drug interaction studies revealed no significant interactions between desirudin and acetylsalicylic acid, heparin, warfarin, DDAVP (a vasopressin analogue). or half-therapeutic prioxicam dose. Desirudin may potentiate the effect of large molecular weight dextrans given in large doses and may cause hemorrhage by impairing platelet function. (See FDA Clinical Pharmacology and Biopharmaceutics Review by S. Roy finalized 3/19/01).

Clinical Studies
The efficacy of desirudin for prophylaxis of deep vein thrombosis in patients undergoing hip replacement is provided by three clinical studies. An additional study was used to help identify the desirudin dose for study. The important design features and study characteristics of these four studies are presented below.

Trial Design Features and Populations Studied

	Study RH/E23 (N=1203[a])	Study RH/E25 (N=2086)	Study RH/E28 (N=452)	Study RH/PT3 (N=48)
Study features:				
Dates	5/92-8/93	4/94-11/95	11/93-8/94	4/91-12/91
R,DB,PG[e] (Yes, No)	Yes	Yes	Yes	No. (Open-label, non-randomized, parallel groups)
Number of centers	17	31	11	1
Multinational	Yes, Europe	Yes, Europe	Two countries (Denmark, Sweden)	Sweden
Control	Heparin (UFH)[c]	Enoxaparin (LMWH)[d]	Heparin (UFH)	Dose-comparative
Dose	Desirudin: 10mg, 15mg or 20mg sc 5min pre-operatively and after surgery in the evening of the same day and then BID for 9 more days. Heparin: 5000U sc 2 hrs pre-op, in the afternoon and evening after surgery followed by TID dosing	Desirudin: 15mg sc within 30min pre-op, then BID for 10 days post-op; Enoxaparin: 40mg sc 12hrs pre-op then qd for to 10 days post-operative.	Desirudin: 15mg sc within 30min pre-op, then BID for 10 days post-op; Heparin: 5000units sc 2 hrs pre-op then TID for 10 days post-op.	Desirudin: 10mg, 20mg, or 40mg 2hrs pre-operatively and after surgery in the evening of the same day and then BID for 9 more days.
Actual duration of dosing, mean (days)	10.4	10.4	8.8	
Primary efficacy endpoint	Composite endpoint essentially same as for RH/E25 except that distal as well as proximal DVT was included.	Composite endpoint consisting of occurrence of one or more of the following: • Positive venogram (central read) with proximal DVT at end of treatment period [bilateral venogram required at end of study treatment for asymptomatic patients] • High probability ventilation/perfusion scan • Autopsy-documented thrombosis • Unexplained death during study drug treatment	Same as for RH/E23	[Study not designed to evaluate efficacy. Main objective was to evaluate safety, particularly bleeding].
Primary efficacy population	Essentially same as for RH/E25	Evaluable population – adequate venogram within designated timeframe and centrally read; ≥80% compliance; no use of disallowed medications	Same as for RH/E25	[Safety study – efficacy endpoint not described]
Study population:				
Age (yrs): Mean Range	 66.3 25-90	 65.5 18-90	 68.4 34-89	 70.6 48-84
Gender, M/F/U (%)[b]	35/58/7	41.6/58.1/0.3	41/57/2	31/69
Important inclusion/exclusion criteria	Similar to RH/E25 except that this study: *required: age >21, *allowed no previous hip surgery on the same side in prior 6mos (as compared to no previous surgery or fracture of lower extremities within prior 3 months for RH/E25) *allowed mild renal impairment up to serum creatinine of 2.0mg/dl (as compared to not allowed to be above upper limit of normal in RH/E25) *no mention of surgical stockings	General: males/females ≥18 yrs weighing at least 50kg undergoing unilateral total hip replacement (cemented or non-cemented prosthesis); no previous surgery or fracture of lower extremities within prior 3 months); no use of other anticoagulants or other possibly interfering medications during 7 days prior to study, no known hemostatic disorders; no recent major surgery; no recent stroke or major bleeding (including intraocular, retroperitoneal, intracranial; no uncontrolled hypertension; no inflammatory bowel disease; no contraindications to study medications or contrast medium; no use of nongraded stockings	Same as for RH/E25	Similar to RH/25 except that this study: *required a first elective total hip replacement *allowed serum creatinine up to 1.5mg/dl (as compared to not allowed to be above upper limit of normal in RH/E25); *no mention of surgical stockings

[a] One patient randomized twice; [b] U=unknown: [c] UFH=unfractionated heparin; [d] LMWH=low molecular weight heparin; [e] R,DB,PG= randomized, double-blind, parallel groups; N=number of patients enrolled

The three controlled clinical efficacy trials all had a similar design. All were multicenter, randomized, double-blind, parallel group, active control studies involving treatment with desirudin twice daily beginning a short time prior to surgery and continued post-operatively for about 8-10 days. The desirudin 15mg subcutaneous BID dose was used in all three studies. The enoxaparin dose and regimen (40mg sc once daily initiated 12 hrs pre-operatively) used as comparator in Study RH/E25 is an approved thromboprophylaxis regimen for enoxaparin in hip replacement surgery. Heparin administered subcutaneously, though widely used for thromboprophylaxis, is not an approved regimen.

The populations of patients in these three trials were similar. All three had a modest preponderance of women (57-69%). All three of these studies were done in Europe and there were very few Black or Oriental patients. Therefore, the study populations do not mirror the U.S. target population in this regard. Inclusion and exclusion criteria were similar.

The open-label, dose-ranging study (RH/PT3) was not designed to evaluate efficacy.

Disposition of Patients: The disposition of patients during the three clinical efficacy studies is summarized in the table below. For inclusion in the primary efficacy analysis patients the protocol required that all patients must have undergone successful venography at the end of study drug treatment. Because venography is an invasive test that can be difficult to perform successfully in all patients, the statistical plan for these studies incorporated a 20-25% excess of patients to allow for "non-evaluable" patients.

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Disposition of Patients in Controlled Clinical Studies

	Number of Patients (%)										
	Study RH/E23					Study RH/E25			Study RH/E28		
	Desirudin 10mg	Desirudin 15mg	Desirudin 20mg	Heparin	Total	Desirudin 15mg	Enoxaparin 40mg	Total	Desirudin 15mg	Heparin	Total
Enrolled					1203			2086			452
Randomized	283	277	282	278	1119[a]	1043	1036	2079	225	220	445
Received study drug and operation	283	277	282	278	1119	1042	1036	2078	225	220	445
Completed	265 (94%)	253 (91%)	248 (88%)	263 (95%)	1029 (92%)	973 (93%)	975 (94%)	1948 (94%)	202 (90%)	193 (88%)	395 (88%)
Discontinued prematurely:	18 (6.4%)	24 (8.7%)	34 (12.1%)	14 (5.1%)	90 (8.0%)	70 (6.7%)	61 (5.9%)	131 (6.3%)	23 (10.2%)	27 (12.3%)	50 (11.2%)
Adverse experience	6 (2.1%)	16 (5.8%)	15 (5.3%)	6 (2.2%)	43 (3.8%)	30 (2.9%)	23 (2.2%)	53 (2.5%)	9 (4.0%)	13 (5.9%)	22 (4.9%)
Protocol violation[b]	2 (0.7%)	2 (0.7%)	8 (2.8%)	0 (0.0%)	12 (1.1%)	7 (0.7%)	13 (1.3%)	20 (1.0%)	10 (4.4%)	8 (3.6%)	18 (4.0%)
Consent withdrawn	5 (1.8%)	2 (0.7%)	2 (0.7%)	4 (1.4%)	13 (1.2%)	14 (1.3%)	11 (1.1%)	25 (1.2%)	3 (1.3%)	5 (2.3%)	8 (1.8%)
Administrative problems	4 (1.4%)	3 (1.1%)	5 (1.8%)	2 (0.7%)	14 (1.3%)	12 (1.2%)	8 (0.8%)	20 (1.0%)	1 (0.4%)	1 (0.5%)	2 (0.4%)
Abnormal lab value	1 (0.4%	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	2 (0.1%)			
Abnormal test procedure	0 (0.0%)	1 (0.4%)	1 (0.4%)	2 (0.7%)	4 (0.4%)	4 (0.4%)	1 (0.1%)	5 (0.2%)			
Trial Rx no longer required	0 (0.0%)	0 (0.0%)	2 (0.7%)	0 (0.0%)	2 (0.2%)	0 (0.0%)	1 (0.1%)	1			
Death	0 (0.0%)	0 (0.0%)	1 (0.4%)	0 (0.0%)	1 (0.1%)	1 (0.1%)	1 (0.1%)	2 (0.1%)			
Patient non-compliance						1 (0.1%)	2 (0.2%)	3 (0.1%)			
Evaluable[c]	213 (75%)	196 (71%)	209 (74%)	219 (79%)	837 (75%)	802 (77%)	785 (76%)	1587 (76%)	174 (77%)	177 (80%)	351 (79%)

[a] one patient enrolled twice [b] Protocol criteria not met [c] for primary efficacy endpoint

reviewer's original table, based on information in sponsor's tables for study reports

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In Study RH/E25 about 94% of patients completed study treatment. About 76% of patients were evaluable for the primary efficacy analysis. Disposition was essentially the same across the two treatments. In Study RH/E28 about 89% of patients completed study treatment and most of these (about 79%) were evaluable for the primary efficacy analysis. Disposition was similar in both treatment groups. About 6-11% of patients discontinued study treatment prematurely. The major reason for premature discontinuation was adverse events (chiefly bleeding) followed by consent withdrawn, failure to meet protocol entry criteria and administrative problems.

Efficacy Evaluation: Event rates for the composite endpoint and components of the composite endpoint in each study are summarized in the following table:

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Efficacy Results for Controlled Clinical Efficacy Studies (Efficacy Evaluable Population)

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
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
Confirmed PE	0/213 (0.0%)	1/196 (0.5%)	0/209 (0.0%)	0/219 (0.0%)		2/802 (0.025%)	2/785 (0.025%)		0/174 (0.0%)	0/177 (0.0%)	
DVT											
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
Distal DVT	33/213 (15.5%)	30/196 (15.3%)	32/209 (15.3%)	32/219 (14.6%)					7/174 (4.0%)	12/177 (6.8%)	
Death	0/213 (0.0%)	0/196 (0.0%)	1/209 (0.5%)	0/219 (0.0%)		1/802 (0.012%)	0/785 (0.0%)		0/174 (0.0%)	0/177 (0.0%)	

sponsor's p-values: 20mg vs. heparin, 0.0001; 15mg vs. heparin, 0.0002; 10mg vs. heparin, 0.0113.

Reviewer's original table, based on sponsor's tables in study reports

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In Study RH/E25 the desirudin 15mg BID group had significantly fewer patients with venous thromboembolic events than the enoxaparin group. Also, fewer desirudin patients had proximal DVT as compared to the enoxaparin patients. Efficacy results were similar in males and females and in both older patients (≥65 yrs) and younger patients (<65yrs). In Study RH/E28 the desirudin 15mg BID group had significantly fewer patients with venous thromboembolic events and fewer patients with proximal DVT than did the enoxaparin group. The result was similar in males and females. With regard to age, though patients 65 years or older in the desirudin group showed a lower VTE event rate than did patients ≥65 years in the enoxaparin group (23/434 (5.3%) vs. 44/452 (9.73%) for desirudin and enoxaparin, respectively; p=0.0083), for patients younger than 65 years the VTE event rate in the desirudin group [16/368 (4.8%)] was similar to that in the enoxaparin group [16/333 (4.35%)], (p=0.7181). There was no apparent treatment by country interaction with regard to the efficacy result. In Study RH/E23 event rates in patients receiving desirudin 15mg BID or 20mg BID were significantly less than the rates in patients receiving heparin or desirudin 10mg.

Study RH/PT3 was a small pilot dose-ranging study used to select the doses of desirudin to be used in the large dose-ranging trial RH/E23. This small study was designed primarily as a safety study. Incidence of venous thromboembolic events was 41.7% (5/12) in the 10mg group, 9% (1/11) in the 15mg group and 10% (2/20) in the 20mg group. Two patients in the 10mg group and 1 patient in the 20mg group suffered a pulmonary embolus.

Safety: The major safety concern for desirudin is bleeding. Hemorrhage rates for the clinical studies in prophylaxis of DVT are summarized in the following table.

Hemorrhage in Clinical Trials in Elective Hip Replacement

Study	Hemorrhage (number of patients, %)					
	Desirudin 10mg	Desirudin 15mg	Desirudin 20mg	Desirudin 40mg	UFH	Enoxaparin
RH/PT3*	0/12 (0.0)%)	1/12 (8.3%)	1/21 (4.8%)[3]	3/3 (100%)[b]		
RH/E23	73/283 (25.8%)	96/277 (34.7%)	95/282 (33.7%)		76 278 (27.3%)	
RH/E 25		155/1028 (15.1%)				198/768 (25.8%)
RH/E28[a]		17/225 (7.6%)			19 220 (8.6%)	
RH/E24[@]		NR			NR	
Total database						
Any hemorrhage	73/295 (24.7%)	464/1561 (29.7%)	98/303 (32.3%)	3/3 (100%)	111/501 (22.2%)	341/1036 (32.9%)
Serious Hemorrhage	8/295 (2.7%)	41/1561 (2.6%)	13/303 (4.3%)	3/3 (100%)	15 501 (3.0%)	21/1036 (2.0%)

* total patients with major bleeding # also 2 with hematoma
[a] hemorrhage, not otherwise specified (NOS)
[b] 3 of 3 patients receiving this dose had major bleeding so the 40mg dose was dropped from the study.
@ This was a study initiated in Canada that was discontinued due to administrative reasons after entry of 10 patients (8 treated); 1 patient experienced DVT and PE; no deaths.
NR=not reported

Reviewer's table, based on sponsor's tables and study reports

There was a higher incidence of patients with hemorrhage in patients receiving desirudin 15mg as compared to heparin (29.7% versus 22.2% of patients, respectively, p=0.001). Generally, incidence and seriousness of hemorrhage increased with increasing desirudin dose. Significantly

greater likelihood of bleeding with desirudin as compared to enoxaparin or heparin was found for patients with the following factors: spinal/epidural anesthesia, diabetes mellitus, obesity, longer surgical duration and concomitant use of NSAIDs, anti-inflammatory medications, anti-platelet medications, plasma expanders and anticoagulants.

In Study RH/E23 extent of anticoagulation of patients during the study was evaluated by assessing effect of treatments on aPTT. Results are summarized in the following table:

Effect of Study Drug Treatment on aPTT in Study RH/E23

	APTT			
	Heparin (N=147)	Desirudin 10mg (N=141)	Desirudin 15mg (N=143)	Desirudin 20mg (N=133)
Baseline				
Mean	37.7	37.8	37.6	38.0
Median	37.1	37.4	36.7	37.6
Range				
Trough:				
Mean	37.3	41.3	42.8	44.3
Median	36.5	40.3	41.1	42.9
Range				
Trough/Baseline				
Mean	0.99	1.09	1.14	1.17
Median	0.98	1.07	1.11	1.14
Range				
	(N=204)	(N=198)	(N=202)	(N=196)
Baseline				
Mean	39.1	39.4	39.6	39.7
Median	37.6	38.0	37.4	37.9
Range				
Peak				
Mean	39.0	49.4	53.9	55.1
Median	37.8	47.7	51.3	52.0
Range				
Peak/Baseline				
Mean	1.01	1.27	1.38	1.42
Median	1.00	1.26	1.37	1.40
Range				

From sponsor's tables

The desirudin treatments caused a significant rise in peak and trough aPTT in a dose-dependent fashion. In contrast, subcutaneous heparin did not significantly affect aPTT. The sponsor's analysis of occurrence of DVT and aPTT did not demonstrate any correlation between the aPTT levels and VTE events or peri-operative or total blood loss. The sponsor did not examine the relationship between aPTT and hemorrhage adverse events.

Incidences of the most frequent, serious and other important adverse events in the Phase II/III studies of desirudin 15mg BID are summarized in the following table:

Adverse Events in Desirudin 15mg BID Studies

	Desirudin 15mg q12hr (N=1561)	Heparin (N=501)	Enoxaparin (N=1036)	p-value[a]	p-value[b]
Hemorrhage					
Any	464 (29.7%)	111 (22.2%)	341 (32.9%)	0.001	
Major	13 (0.8%)	0 (0.0%)	2 (0.2%)		
Serious	41 (2.6%)	15 (3.0%)	21 (2.0%)		
Most frequent events:					
Hemorrhage NOS[c]	365 (23%)	79 (16%)	268 (26%)	<0.001	
Nausea	193 (12%)	47 (9%)	121 (12%)		
Arthralgia	151 (10%)	6 (1.0%)	146 (14%)	<0.001	<0.001
Anemia	138 (9%)	37 (7%)	117 (11%)		
Wound secretion	139 (9%)	29 (6%)	82 (8%)	0.030	
Insomnia	137 (9%)	22 (4%)	134 (13%)	0.001	<0.001
Most frequent serious events:					
Hemorrhage NOS[c]	44 (3%)	18 (4%)	18 (2%)		
Hematoma	10 (<1%)	1 (<1%)	4 (<1%)		
Immunologic and allergic reactions:					
Any event	25 (2%)	6 (1%)	12 (1%)		
Allergic reaction	5 (<1%)	1 (<1%)	1 (<1%)		
Allergy	5 (<1%)	0	6 (<1%)		
Anaphylactic shock	0	1 (<1%)	0		
Rhinitis	0	1 (<1%)	0		
Dermatitis	3 (<1%)	1 (<1%)	1 (<1%)		
Dermatitis contact	6 (<1%)	1 (<1%)	4 (<1%)		
Urticaria	6 (<1%)	1 (<1%)	1 (<1%)		
Allergic reaction with positive skin prick test	1/2	0/2	0/2		
Deaths[d]:					
During treatment	1 (<1%)	0	1 (<1%)		
During followup (6 weeks)	3 (<1%)	3 (<1%)	1 (<1%)		
Premature study discontinuation:					
Any cause	122 (8%)	45 (9%)	61 (6%)		
Due to adverse experience	55 (4%)	20 (4%)	23 (2%)		
Death	1 (<1%)	0	1 (<1%)		
Most frequent events leading to study discontinuation:					
Hemorrhage NOS	17 (1%)	6 (1%)	1 (<1%)		
Hematoma	5 (<1%)	1 (<1%)	2 (<1%)		
Edema legs	4 (<1%)	0	1 (<1%)		
Cerebrovascular disorder	4 (<1%)	0	0		
Hypotension	3 (<1%)	0	0		

[a] desirudin vs. heparin [b] desirudin vs. enoxaparin; [c] NOS=not otherwise specified;
[d] During treatment one desirudin patient died of hypotension and one enoxaparin patient died of myocardial infarction. During followup one enoxaparin patient died of cardiovascular disease NOS; one desirudin patients died of pulmonary embolism, 1 of cardiovascular collapse, 1 of cerebral hematoma. One heparin patient died of pulmonary emphysema and bronchopneumonia, 1 of cerebral infarction, and one of thrombcytopenia, septic shock, adrenal hemorrhage and peritonitis.

reviewer's table, based on information in sponsor's tables

Events appearing significantly more commonly in desirudin-treated patients as compared to those receiving unfractionated heparin included: injection site mass, wound secretion, hypertension, hypotension, deep thrombophlebitis, constipation, vomiting, nonspecific hemorrhage, hypovolemia, arthralgia, headache, insomnia, and urinary retention. Events appearing

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-271

Aventis Pharmaceuticals
c/o Quintiles, Inc.
Attention: Philip Kastner, Ph.D.
P.O. Box 9708 (Dock 6, F3-M3026)
Kansas City, MO 64134-0708

Dear Dr. Kastner:

Please refer to your new drug application (NDA) dated June 28, 2000, received July 14, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for [redacted] [desirudin [redacted] for injection].

We acknowledge receipt of your submissions dated September 12 and 13, October 11, November 14, and December 19, 2000, January 15 and 23, March 2, 5, 19, 23, and 27, 2001.

We have completed the review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following:

Chemistry, Manufacturing, and Controls

Provide an acceptable response to our Discipline Review Letter dated April 16, 2001.

Nonclinical Pharmacology and Toxicology

We reiterate the request stated in our letters dated September 1 and December 15, 2000. Conduct a subacute, subcutaneous, 4-week toxicity study in rhesus monkeys and submit its full report for review and evaluation.

Clinical

We have safety concerns regarding the proposed 2-count carton. The carton is labeled as [redacted] 15 mg and it may be mistaken that the total content of the 2-count carton is 15 mg of the active drug. We recommend packaging [redacted] and 10-count cartons.

In addition, it will be necessary for you to submit revised draft labeling for the drug. The labeling should be identical in content to the enclosed labeling (text for the package insert). It will also become necessary for you to revise the immediate container and carton labeling submitted June 28, 2000 as follows:

significantly more commonly in desirudin-treated patients as compared to those receiving enoxaparin included: injection site mass, arthralgia, headache, and insomnia. More patients who received enoxaparin experienced anemia than did patients who received desirudin. No significant differences between treatment groups were seen in adverse events reported during the post-treatment followup period.

With regard to clinical laboratory studies, other than changes in hemoglobin/hematocrit reflecting blood loss, there appeared to be no significant changes over the time of treatment. Some patients had some elevation of hepatic transaminases, but this increase tended to be less common with desirudin than with heparin.

Special Populations: The population studied in the efficacy trials for this application did not include significant numbers of patients with clinically important renal impairment or hepatic impairment. A pharmacokinetic study in patients with renal failure indicated a prolonged $AUC_{0\text{-}60hr}$ for aPTT in subjects with moderate or severe renal failure and adjustment of desirudin dose is needed in these patients. (See FDA Clinical Pharmacology and Biopharmaceutics Review by S. Roy finalized 3/19/01). The sponsor should address handling of desirudin in patients with hepatic insufficiency.

Conclusions and Recommendations:
Substantial information has been provided to support the effectiveness and safety of desirudin 15mg administered within 30 minutes prior to surgery and then post-operatively twice daily (q12hr) for 8 to 12 days for prophylaxis of deep vein thrombosis which may lead to pulmonary embolus in adult patients undergoing elective hip replacement surgery.

Efficacy: Evidence for effectiveness comes from two clinical trials in European populations involving a total of 3741 patients 2110 of whom received desirudin. In Study RH/E28 desirudin 15mg BID was shown to be significantly more effective in reducing the incidence of VTE than subcutaneously administered unfractionated heparin in these patients (7.5% vs 23.2% for desirudin and heparin, respectively, 2-sided p-value=0.0001). Study RH/E25 showed that desirudin 15mg BID was significantly more effective than enoxaparin 40mg sc daily in reducing the incidence of VTE in these patients (4.86% vs. 7.64% for desirudin and heparin, respectively, 2-sided p-value=0.018). The benefit in reducing the likelihood of VTE is apparent for proximal DVT as well as for total VTE. Additional support for effectiveness of desirudin comes from Study RH/E23, a dose-finding efficacy trial.

The statistical analyses specified in the protocols for these studies planned primary analysis of an "efficacy evaluable" population, which consisted of all patients who received study medication, underwent surgery and had an evaluable venogram at conclusion of study (or for cause during study). About 20-25% of patients randomized were not evaluable for efficacy by these criteria. Nevertheless, the distributions of these non-evaluable patients and their characteristics were similar across treatment groups for both the controlled efficacy trials and the double-blind, controlled, dose-ranging study. No efficacy analysis was done using all patients randomized who were received study medication and underwent surgery. Calculation of the VTE event rates for Studies RH/E23, RH/E25 and RH/E28 using this population gives the following results. (In this

analysis patients are considered as no event if efficacy data [mainly venogram] is missing). This analysis showed similar results to the sponsor's analysis of efficacy evaluable patients. This analysis is more consistent with the analyses of efficacy data displayed in the labeling for low molecular weight heparins (LMWH) (e.g., enoxaparin, dalteparin) already approved for this indication. It would be desirable to display similarly analyzed study results for all the anticoagulants approved for prevention of DVT in hip replacement surgery.

APPEARS THIS WAY
ON ORIGINAL

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

Though the population in which desirudin was studied does not reflect the U.S. population in terms of racial and ethnic diversity, it is reasonable to anticipate that desirudin will have an anticoagulant effect in the U.S. population. A pharmacokinetic study (R13/1993) in Japanese healthy volunteers showed similar results to those in healthy Caucasian subjects. The management of patients in the European trials appears to be similar to management of hip surgery patients in the U.S. and thus the drug can reasonably be expected to be effective in the U.S. population. However, there may be quantitative differences in event rates and bleeding complications between these two populations. Therefore, it would be prudent to examine effects of desirudin in subjects from significant U.S. minority ethnic groups.

Because elective hip replacement is rare in pediatric patients, desirudin for this indication is not pertinent to the pediatric population. The sponsor had requested waiver of requirement to conduct pediatric studies and this waiver should be granted.

Safety:
A total of 1561 patients have received desirudin 15mg sc BID in clinical studies of the drug. Of these, 92.2% completed desirudin treatment as planned. The major reason for treatment withdrawal was adverse events (mainly bleeding). Bleeding appeared to be more common in patients treated with desirudin 15mg BID than in patients treated with subcutaneous unfractionated heparin. Risk of bleeding with desirudin appeared to be increased in patients undergoing spinal/epidural anesthesia and also but less markedly with other factors such as obesity, diabetes mellitus, and use of other medicines that interfere with coagulation. The labeling for desirudin should reflect these safety concerns and include a black box warning regarding spinal/epidural anesthesia. Death and serious adverse events other than bleeding were uncommon in the clinical studies.

Because the half-life of desirudin is significantly prolonged in patients with moderate or severe renal failure, adjustment of dose is necessary for these patients. Handling of desirudin by patients with hepatic impairment should be examined in the post-marketing period.

The sponsor's proposed labeling provides some instructions for switching patients from desirudin to longer term oral anticoagulation (e.g., with warfarin) should this be required. The sponsor should be requested to provide clinical information to support the recommendations proposed for this situation. Also, clinical information should be provided for switching patients from other anticoagulants to desirudin. In the clinical trials other anticoagulants were discontinued for several days prior to initiating desirudin.

Desirudin produced congenital malformations in rat and rabbit teratogenicity studies. Thus, it is a Pregnancy Category C drug. (Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans). Desirudin should be

used in pregnant women only if the benefit outweighs the potential risk. The labeling should reflect this information.

cc:
NDA
HFD-180
HFD-180/LTalarico
HFD-180/KRobie-Suh
HFD-180/BStrongin
HFD-180/JChoudary
HFD-180/LZhou
HFD-720/TPermutt
f/t 5/11/01krs

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/

Kathy Robie-Suh
5/14/01 09:53:23 AM
MEDICAL OFFICER

Lilia Talarico
5/14/01 04:39:12 PM
MEDICAL OFFICER

APPEARS THIS WAY
ON ORIGINAL

(u)

Number of Pages Redacted # 24

❖❖❖

Draft Labeling
(not releasable

This section (DSI memo regarding GLP inspections) is not applicable.

S 3-7-03

Alice Kacuba

APPEARS THIS WAY
ON ORIGINAL

This section (carcinogenicity stat review) is not applicable.

/S/ /S/ 3-7-03

Alice Kacuba

APPEARS THIS WAY
ON ORIGINAL

This section (CAC/ECAC committee correspondence) is not applicable.

/S/

3-7-03

Alice Kacuba

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(V)

Number of Pages Redacted 7

❖❖❖

Confidential,
Commercial Information

MEMORANDUM OF TELECON

DATE: January 26, 2001

APPLICATION NUMBER: NDA 21-271, [redacted] [desirudin [redacted] for Injection]

BETWEEN:

Name: Philip R. Kastner, Ph.D., Associate Director, Regulatory and Technical Services, Quintiles, Inc.
Phone: (816) 767-6685
Representing: Aventis Pharmaceuticals, Inc.

AND

Name: Brian Strongin, Regulatory Health Project Manager
Division of Gastrointestinal & Coagulation Drug Products, HFD-180

SUBJECT: Questions Regarding the Division's Request to Conduct a Toxicology Study in Monkeys

Background

NDA 21-271, submitted June 28, 2000, received July 14, 2000, provides for prevention of deep venous thrombosis which may lead to pulmonary embolism in patients undergoing elective hip replacement surgery. In information request letters dated September 1 and December 15, 2000, the Division requested that the sponsor conduct a subacute one-month subcutaneous toxicology study in monkeys and provide the final report for review and evaluation. In their January 23, 2001 response to our December 15 letter, the firm agreed to begin the study in June, 2001 and posed the following questions: (1) Please confirm that the study is to be conducted in rhesus monkeys; and (2) Please confirm that providing the results of this monkey study will not impact the ongoing evaluation of the submitted data in the NDA and the determination for approval of the NDA.

Today's Call

The Division's responses to the firm's questions were provided in today's call.

1. *Please confirm that the study is to be conducted in rhesus monkeys.*

   The study is to be conducted in rhesus monkeys.

2. *Please confirm that providing the results of this monkey study will not impact the ongoing evaluation of the submitted data in the NDA and the determination for approval of the NDA.*

   It is premature to comment on the possible effect on the pending action for this review cycle. Submission of the study report after the user fee due date (10-month due date is May 14, 2001) may impact the action to be taken.

I also confirmed that all reviews are in progress and will continue. The call was then terminated.

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM OF TELECON

DATE: January 8, 2001

APPLICATION NUMBER: NDA 21-271, [redacted] [desirudin [redacted] for Injection]

BETWEEN:

Name: Phillip Kastner, Ph.D., Associate Director, Regulatory and Technical Services
Phone: (816) 767-6685
Representing: Quintiles, Inc. representing Aventis Pharmaceuticals, Inc.

AND

Name: Brian Strongin, Project Manager
Division of Gastrointestinal & Coagulation Drug Products, HFD-180

SUBJECT: Request for a Copy of the OPDRA Consultation Response Regarding the [redacted] Tradename

Background

NDA 21-271, submitted June 28, 2000, received July 14, 2000, provides for prevention of deep venous thrombosis which may lead to pulmonary embolism in patients undergoing elective hip replacement surgery. The proposed tradename, [redacted] was consulted to the Office of Post-Marketing Drug Risk Assessment (OPDRA) for review July 25, 2000. The OPDRA review, dated November 13, 2000, recommended against use of the proposed tradename and cited the possibility of confusion with other tradenames such as Prevacid and Norvasc. On Friday, January 5, 2001 the Division received a request from Dr. Kastner requesting a copy of the OPDRA review. On January 5, I e-mailed Jerry Philips of OPDRA to ask if they have a policy regarding sending reviews to the sponsor. His January 8 reply cited a CDER policy to not send reviews to sponsor's prior to an applications approval. He suggested we provide enough information to the sponsor to tell them the reasons for our objection to their tradename.

Today's Call

I explained that it was not the usual practice of OPDRA or CDER to release reviews prior to an application's approval unless the review was part of an Advisory Committee background package. In that case, the review would be redacted by the Freedom of Information Office prior to its release. I explained that the review discussed OPDRA's tradename process including expert panel discussions, written and verbal prescription studies, and a safety evaluator risk assessment. Based on this process, OPDRA concluded that the potential for confusion between the proposed tradename, [redacted] and existing tradenames such as Prevacid or Norvasc exists and recommended against use of the tradename. The call was then concluded.

/S/

1/8/01

Brian Strongin
Project Manager

/s/

Brian Strongin
1/8/01 11:58:59 AM
CSO

APPEARS THIS WAY
ON ORIGINAL

/s/

Brian Strongin
3/9/01 12:35:46 PM
CSO

APPEARS THIS WAY
ON ORIGINAL

[redacted] 14

MAR 2 [illegible] 2001

21-271

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: 2-27-2001

TO: Julieann DuBeau, Regulatory Project Manager
Ann Farrell, Clinical Reviewer
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

THROUGH: John Martin, M.D., Chief
Good Clinical Practice Branch 1
Division of Scientific Investigations

FROM: Khairy W. Malek, M.D.

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-271

APPLICANT: Aventis Pharmaceutical Inc.

DRUG: [redacted] (desirudin [redacted]) for injection)

INDICATION: [redacted]

CONSULTATION REQUEST DATE: 10-6-2000

ACTION GOAL DATE: May 14, 2001

I. BACKGROUND:

The aim of the study was to compare the efficacy and safety of this new antithrombotic agent compared to LMWH (low molecular weight heparin (enoxaparin)) in preventing DVT, PE, and death due to PE. The inspection targeted verification of efficacy end points by bilateral ascending phlebography, ventilation/perfusion lung scan or pulmonary angiography. Attention was also on adverse reactions especially haemorrhage and comparing the CRFs with source documents.

II. RESULTS (by protocol/site):

NAME	CITY	Country	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION
[redacted]	[redacted]	[redacted]	10-6-00	2-22-01	VAI
[redacted]	[redacted]	[redacted]	10-6-00	2-22-01	NAI

A. Protocol # RH/E25

1. Site [redacted] Data acceptable

a. We reviewed the records of 141subjects out of 168 enrolled in the study.

b. The principal investigator, [redacted] retired and was not available. The sub-investigator, [redacted] was available during the inspection.

c. Violations observed were mainly protocol violations. Two nephrectomized subjects were included contrary to the protocol exclusion criteria. A serious bleeding episode was initially not reported, but was subsequently reported and recorded in the sponsor's final report.

2. Site: [redacted]

a. We reviewed the records of all 52 subjects in the study. The principal investigator was available at the site.

b. There were no limitations to our inspection.

c. No regulatory violations were established.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

These violations found should not affect the integrity of the data presented in support of the NDA

/S/

Khairy W. Malek, M.D., Ph.D.
GCPB 1 reviewer

CONCURRENCE:

/S/

John Martin, M.D., Chief
Good Clinical Practice Branch 1
Division of Scientific Investigations

DISTRIBUTION:
NDA # 21-271
Division File
HFD-45/Program Management Staff (electronic copy)
HFD-47/Currier
HFD-46/47/GCP 1 Branch Chief: Martin
HFD-46/47/GCPB File # 10295 and 10294
HFD-46/47/Reading File

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAR - 9 2001

Docteur Michel Fouche
Chirurgie Orthopedique
Polyclinique Sevigne
Rue Du Chene Germain
35510 Cesson- Sevigne
France

Dear Dr. Fouche:

Between January 22 and 26, 2001, Mr. Joel Martinez and Dr. Khairy Malek, representing the U.S. Food and Drug Administration (FDA), met with you to review your conduct of a clinical study (Protocol # RH/E 25) of the investigational drug, [redacted] (desirudin [redacted] for injection), performed for Aventis Pharmaceuticals Inc. This study was not conducted under a U.S. Investigational New Drug Application (IND). This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections, designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

Based on our review of this inspection report and the documents submitted with that report, we conclude that you did adhere to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown to the FDA Investigators during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours,

[redacted]

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, Maryland 20855

cc:
HFA-224
HFD-180 Doc.Rm. NDA# 21-271
HFD-180 Review Div.Dir. Talarico
HFD-180 MO Farrell
HFD-180 PM DuBeau
HFD-45 Reading File
HFD-46 Chron File
HFD-46 GCP File # 10294
HFD-46 GCP Reviewer Malek
HFD-46 GCP-1 Br. Chief Martin
HFD-46 CSO Huff
HFR-SW150 DIB Thornburg
HFR-SW1540 Bimo Monitor Martinez
HFR-SW1540 Field Investigator Martinez
HFC-134 Kadar

Field Classification: VAI

Headquarters Classification:

__X__1)NAI
_____2)VAI-no response required
_____3)VAI-response requested
_____4)OAI
Deficiencies noted:

_____ inadequate informed consent
_____ inadequate drug accountability
_____ failure to adhere to protocol
_____ inadequate records
_____ failure to report ADRS

O:\JRM\Fouche.doc
Drafted: KM 2/27/01
Revised: JMartin 3/8/01
Final type:jau:3/9/01

Note to Review Division and DSI Recommendation
The records of all 52 subjects included in the study were reviewed. No violations of FDA regulations were established. The data from this study appear acceptable for use in support of the NDA.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAR - 9 200

Dr. Josef Hochreiter
A. O. Krankenhaus d. Barmherzigen Schwestern Linz
Seilersträtte 4
A-4010 Linz
Austria

Dear Dr. Hochreiter:

Between January 15 and 19, 2001, Mr. Joel Martinez and Dr. Khairy Malek representing the U.S. Food and Drug Administration (FDA), reviewed the conduct of a clinical study (Protocol # RH/E 25) of the investigational drug, ——— (desirudin ———) for injection), performed for Aventis Pharmaceuticals, Inc. This study was not conducted under a U. S. Investigational New Drug application. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

At our initial contact, we learned that ——— had retired in 1996, after this study had been completed, and that you assumed responsibility for this study at that time. At the conclusion of the inspection, Mr. Martinez presented the inspectional observations listed on Form FDA-483 and discussed them with you. We have completed our evaluation of the inspection report, and your letter of response to Dr. Attila Kadar, FDA/DEIO, dated February 6, 2001. We accept your explanations as described in your response.

We appreciate the cooperation you have shown to Investigators Joel Martinez and Dr. Malek during the inspection. Should you have any questions or concerns regarding this letter or the inspection, please contact me by letter at the address given below.

Sincerely yours. /S/

John R. Martin, M.D.
Branch Chief
Good Clinical Practice I, HFD-46
Division of Scientific Investigations
Office of Medical Policy
Center for Drug Evaluation and Research
7520 Standish Place, Room 125
Rockville, Maryland 20855

cc:
HFA-224
HFD-180 Doc.Rm. NDA# 21-271
HFD-180 Review Div.Dir. Talarico
HFD-180 MO Farrell
HFD-180 PM DuBeau
HFD-45 Reading File
HFD-46 Chron File
HFD-46 GCP File # 10295
HFD-46 GCP Reviewer Malek
HFD-46 GCP-1 Br. Chief Martin
HFD-46 CSO Huff
HFR-SW150 DIB Thornburg
HFR- SW1540 Bimo Monitor Martinez
HFR-SW1540 Field Investigator Martinez
HFC-134 Kadar

Field Classification: VAI

Headquarters Classification: VAI-RR

_____1)NAI
_X__2)VAI-RR (response received)
_____3)VAI-response requested
_____4)OAI

Deficiencies noted:

_____ inadequate informed consent
_____ inadequate drug accountability
_X___ failure to adhere to protocol
_____ inadequate records
_X ___ failure to report ADRS
O:\JRM\Hochreiter-_ _ _ _ _ _doc
Drafted KM 2/27/01 Final type JAU 3/9/01
Revised JM 3/8/01
Note to Review Division and DSI Recommendation
The records of 141 subjects out of 168 included in the study were reviewed. Violations found were inclusion of two nephrectomised subjects against the protocol exclusion criteria, and failure to initially report a serious peri-operative bleeding, which was later recorded in the sponsor's final report. We believe that these violations will not affect the reliability of the data. The data from this study appear acceptable in support of the NDA.

D.S.

4.1.2.1. Identification of the manufacturing, testing and warehousing sites

1. Drug Substance manufacturing, testing, release, and stability is conducted at:

Novartis Pharma AG
Lichtstrasse 35
CH-4002, Basel
Switzerland

There is no shared manufacturing associated with rHirudin (CGP 39393) production. See note under 4.1.2.2.2.

2. Drug Substance is warehoused and distributed from:

Novartis Pharma S.A.
Site Industriel de Huningue
26, rue de la Chapelle
68333 Huningue Cedex
France

4.1.2.2. Facility Description

The following information has been taken from Novartis Pharma AG site master file attached in the appendices of the CMC section of the NDA.

4.1.2.2.1. Product Flow Diagrams

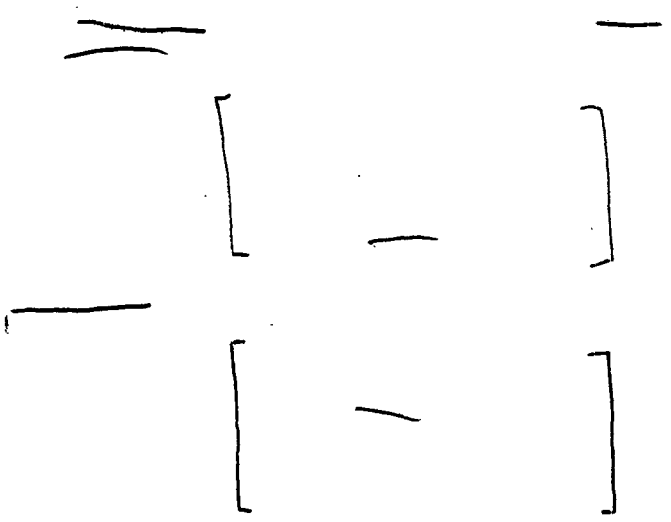
Diagram 1 to 22 show the rHirudin personnel, material and product flow. The room designations are listed on the diagrams.

APPEARS THIS WAY
ON ORIGINAL

D.P.

4.2.3. Manufacturers

4.2.3.1. Identification of the manufacturing sites



The testing, and final release, of both [redacted] and mannitol bulks will be performed by:

Novartis Pharma AG
Lichtstrasse 35
CH-4056, Basel
Switzerland

Drug Product testing for Chromogenic assay is performed at:

Novartis Pharma AG
Lichtstrasse 35
CH-4056, Basel
Switzerland

Drug Product testing for stability for water is performed at:

Solvias AG*
Wissenschaftlich und technische Dienstleistungen
Klybeckstrasse 191
Postfach 4002 Basel
4058 Basel BS

* formerly known as Novartis Services

[redacted]

Subsequently, the product will be shipped to the following facility for labeling and secondary packaging of both [redacted] vials and mannitol ampoules:

Laboratoires Fison SA *
Boulevard Industriel
76580 Le-Trait
France
* an Aventis Pharmaceuticals Products Inc. company

Drug Product stability testing is conducted at:

Novartis Pharma AG
Lichtstrasse 35
CH-4056, Basel
Switzerland

APPEARS THIS WAY
ON ORIGINAL

The Methods Validation Package has not been sent out to the FDA laboratories yet.

/S/

3-7-03

Alice Kacuba

APPEARS THIS WAY
ON ORIGINAL

Specifications, Methods, and Validation for Drug Substance and Drug Product

Drug Substance and Drug Product Analytical Methods Validation

The analytical methods listed in section 4.5.5 Drug Substance and Drug Product Specifications have been validated. The corresponding analytical methods validation reports are included in this section.

APPEARS THIS WAY
ON ORIGINAL

1. Please provide batch numbers and analytical test results for all batches used in clinical and preclinical studies and identify the batches used in pivotal clinical studies. Provide actual numbers for impurity levels, not just a designation of pass/fail.

2. Please provide additional stability data for the primary stability batches. The 12-month data that have been submitted are insufficient to support the proposed 24-month expiration.

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 21-271

INFORMATION REQUEST LETTER

Aventis Pharmaceuticals Inc.
C/O: Quintiles, Inc.
Attention: Philip Kastner, Ph.D.
P.O. Box 9708 (Dock 6, F3-M3026)
Kansas City, MO 64134-0708

Dear Dr. Kastner:

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

We have completed our review of your proposed proprietary name, [redacted], and find the proposed name unacceptable 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).

Please submit an alternate proposed proprietary name for [redacted]. We need your prompt written response to continue our evaluation of your NDA.

If you have any questions, call Julieann DuBeau, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

Kati Johnson
Supervisory Consumer Safety Officer
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

DuBeau

NDA 21-271

INFORMATION REQUEST LETTER

Aventis Pharmaceuticals
Attention: Edmond Roland, M.D.
500 Arcola Road
Collegeville, PA 19426

SEP - 1 2000

Dear Dr. Roland:

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

We are reviewing the Chemistry, Manufacturing, and Controls (CMC), clinical, and preclinical sections of your submission and have the following comments and information requests. We need your prompt written response to continue our evaluation of your NDA.

(1) Provide a list of all manufacturing facilities and a statement as to their readiness for inspection.
(2) Provide a copy of the current European Union (EU) package insert.
(3) State the exact location of gender and age safety and efficacy analyses (i.e., volume and page number).
(4) Provide race safety and efficacy analyses. Or alternatively, provide a written justification for not performing race safety and efficacy analyses.

[redacted]

If you have any questions, call Julieann DuBeau, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

Kati Johnson
Supervisory Consumer Safety Officer
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 21-271
HFD-180/Div. Files
HFD-180/J.DuBeau
HFD-180/Robie-Suh
HFD-180/Farrell
HFD-180/Choudary
HFD-820/DNDC Division Director
DISTRICT OFFICE
R/d Init: Johnson 8/31/00
R/d Init: Choudary 9/1/00
R/d Init: Farrell 8/31/00
JD/August 31, 2000 (drafted)
JD/9/1/00/c:\mydocs\nda\21271008-IR-ltr.doc

/S/ 9/1/00

INFORMATION REQUEST (IR)

APPEARS THIS WAY
ON ORIGINAL

(W)

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

10

This firm is not on the AIP list.

/S/ 3-7-03

Alice Kacuba

This is not a Subpart H application, thus the request for advertising materials is in the Approval letter.

/S/ 3-7-03

Alice Kacuba

Dubeau

MEMORANDUM

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

Date: September 19, 2000

To: Khairy Malek, M.D., GCPB Reviewer/HFD-46

Through (optional): Stan Woollen, M.D., Acting Director, DSI, HFD-45
Lilia Talarico, M.D., Director, HFD-180 9-19-00

From: Julieann DuBeau, Regulatory Health Project Manager, HFD-180 /S/ 9/19/00

Subject: **Request for Clinical Inspections**
NDA 21-271
Aventis Pharmaceuticals
[redacted] [desirudin [redacted] for Injection]

Protocol/Site Identification:

The following protocols/sites essential for approval have been identified for inspection. These sites are listed in order of priority.

Indication	Protocol #	Site (Name and Address)
Prevention of DVT, which may lead to PE, in patients undergoing elective hip replacement surgery	RH/E25	[redacted]
Prevention of DVT, which may lead to PE, in patients undergoing elective hip replacement surgery	RH/E25	

Note: International inspection requests or requests for five or more inspections require sign-off by the ORM Division Director and forwarding through the Director, DSI.

International Inspections:

We have requested inspections because (please check appropriate statements):

____ There are insufficient domestic data

__X__ Only foreign data are submitted to support an application

____ Domestic and foreign data show conflicting results pertinent to decision-making

____ There is a serious issue to resolve, e.g., suspicion of fraud, scientific misconduct, or significant human subject protection violations.

____ Other: SPECIFY

Goal Date for Completion:

We request that the inspections be performed and the Inspection Summary Results be provided by (inspection summary goal date) **April 2, 2001**. We intend to issue an action letter on this application by (action goal date) **May 14, 2001**.

Should you require any additional information, please contact Julieann DuBeau.

Concurrence: (if necessary)
Dr. Kathy Robie-Suh, Medical Team Leader
Dr. Ann Farrell, Medical Reviewer

cc:
Archival NDA 21-271
HFD-180/Division File
HFD-180/RPM/J.DuBeau
HFD-180/Talarico 9/13/00
HFD-180/Robie-Suh 9/13/00
HFD-180/Farrell 9/12/00
HFD-46/GCPB Reviewer/Malek Khairy
HFD-45/Matthew Tarosky
JD/September 12, 2000 (drafted)
JD/9/19/00/c:\mydocs\cons\21271009-dsi-consult.DOC

MEMORANDUM (Request for Clinical Inspections)

/S/

NDA 21-271

AUG - 3 2000

Aventis Pharmaceuticals
Attention: Edmond Roland, M.D.
500 Arcola Road
Collegeville, PA 19426

Dear Dr. Roland:

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

You were notified in our letter dated July 6, 2000, that your application was not accepted for filing due to non-payment of fees. This is to notify you that the Agency has received all fees owed and your application has been accepted as of July 14, 2000.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on September 12, 2000, in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be May 14, 2001, and the secondary user fee goal date will be July 14, 2001.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will make a determination whether to grant or deny a request for a waiver of pediatric studies during the review of the application. In no case, however, will the determination be made later than the date action is taken on the application. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov/cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" (PPSR) in addition to your plans for pediatric drug development described above. We recommend that you submit a Proposed Pediatric Study Request within 120 days from the date of this letter. If you are unable to meet this time frame but are interested in pediatric exclusivity, please notify the division in writing. FDA generally will not accept studies submitted to an NDA before issuance of a Written Request as responsive to a Written Request. Sponsors should obtain a Written Request before submitting pediatric studies to an NDA. If you do not submit a PPSR or indicate that you are interested in pediatric exclusivity, we will review your pediatric drug development plan and notify you of its adequacy. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity. FDA does not necessarily ask a sponsor to complete the same scope of studies to qualify for pediatric exclusivity as it does to fulfill the requirements of the pediatric rule.

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-7310.

Sincerely,

Julieann DuBeau, RN, MSN
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 21-271
HFD-180/Div. Files
HFD-180/J.DuBeau
HFD-180/Reviewers and Team Leaders
DISTRICT OFFICE
HFD-005/Friedman
HFD-094/Rowland
JD/July 20, 2000 (drafted)
JD/8/3/00/c:\mydocs\nda\21271007-ack-after-UN.doc

8/3/00

ACKNOWLEDGEMENT (AC)

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

REQUEST FOR CONSULTATION

TO (Division/Office): Dr. Peter Cooney, HFD-805, Rm 18B-08			FROM: HFD-180 (Division of Gastrointestinal and Coagulation Drug Products) Julie DuBeau, rm 6B17	
DATE: July 21, 2000	IND NO.:	NDA NO.: 21-271	TYPE OF DOCUMENT: NDA (original submission)	DATE OF DOCUMENT: June 28, 2000
NAME OF DRUG: [redacted] desirudin) Injection	PRIORITY CONSIDERATION: Standard		CLASSIFICATION OF DRUG:	DESIRED COMPLETION DATE: March 14, 2001

NAME OF FIRM: Aventis Pharmaceuticals

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)*: See Below

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER:	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER:

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL ☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS: Please review this original NDA. The primary FDAMA goal date is May 14, 2001. The secondary FDAMA goal date is July 14, 2001. The 45 day filing meeting is scheduled for August 28, 2000. Please let me know who the reviewer will be so he/she can be invited to the filing meeting. The filing date is September 12, 2000. Attached are volumes 1.1 to 1.13 (the entire CMC section of the NDA) for your convenience. Thanks.

cc: Original NDA 21-271
HFD-180/Div. Files
HFD-180/DuBeau
HFD-180/Kowblansky

SIGNATURE OF REQUESTER:	3-8423	METHOD OF DELIVERY (Check one): ☐ MAIL ☒ HAND
SIGNATURE OF RECEIVER:		SIGNATURE OF DELIVERER:

JDS 7/24

DuBeau

NOV 13 2000

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: July 25, 2000	**DUE DATE:** March 14, 2001	**OPDRA CONSULT #:** 00-0208

TO: Lilia Talarico, M.D.
Director, Division of Gastro-Intestinal and Coagulation Drug Products
HFD-180

THROUGH: Julie DuBeau, Project Manager
HFD-180

PRODUCT NAME: — [desirudin — for Injection] **NDA #:** 21-271	**DISTRIBUTOR:** Aventis Pharmaceuticals Products Inc.

SAFETY EVALUATOR: Jennifer Fan, Pharm.D.

SUMMARY: In response to a consult from the Division of Gastrointestinal and Coagulation Drug Products (HFD-180), OPDRA conducted a review of the proposed proprietary name — to determine the potential for confusion with approved proprietary and generic names as well as pending names.

OPDRA RECOMMENDATION:
OPDRA does not recommend the use of the proprietary name — (See review).

[/s] 11/13/2000

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

[/s] 11/14/00

Martin Himmel, M.D.
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

NDA 21-271

JUL 6 2000

Aventis Pharmaceuticals
Attention: Edmond Roland, M.D.
500 Arcola Road
Collegeville, PA 19426

Dear Dr. Roland:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: [redacted] desirudin) Injection

Date of Application: June 28, 2000

Date of Receipt: June 28, 2000

Our Reference Number: NDA 21-271

We note that you are in arrears for payment of fees for products, or establishments, or previously submitted applications. Because an application is considered incomplete and can not be accepted for filing until all fees owed have been paid, review of the application referenced above may not begin at this time. Upon receipt of the outstanding fees, we will start the user fee clock and commence review of your application. Payment should be submitted to the following address:

Food and Drug Administration
P.O. Box 360909
Pittsburgh, PA 15251-6909

Checks sent by courier should be delivered to:

Mellon Bank
Three Mellon Bank Center
27th Floor (FDA 360909)
Pittsburgh, PA 15259-0001

NOTE: This address is for courier delivery only. Make sure the FDA Post Office Box Number (P.O. Box 360909) and user fee identification number are on the enclosed check.

Please cite the NDA number listed above at the top of the first page of any communications

concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Gastrointestinal and Coagulation Drug Products, HFD-180
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, call me at (301) 827-7310.

Sincerely,

Julieann DuBeau, RN, MSN
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 21-271
HFD-180/Div. Files
HFD-180/J.DuBeau
HFD-180/Reviewers and Team Leaders
DISTRICT OFFICE
JD/July 6, 2000 (drafted)
JD/7/6/00/c:\mydocs\nda\21271007-UN-ltr.doc

7/6/00

UNACCEPTABLE FOR FILING (UN)