CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020807

ADMINISTRATIVE DOCUMENTS/CORRESPONDENCE

BEHRING

TRADE NAME:	**Refludan**
GENERIC NAME:	**Lepirudin**
DOSAGE FORM:	**Sterile white powder for injection**
STRENGTHS:	**50 mg**
PATENT NO.	**US Patent No. 5,180,668**
EXPIRATION DATE:	**January 19, 2010**
TYPE OF PATENT:	**Drug**
PATENT OWNER:	**Hoechst AG, Frankfurt/Main, Germany**
US REPRESENTATIVE OF THE PATENT OWNER:	**Hoechst Marion Roussel Inc. 10236 Marion Park Drive Kansas City, MO 64137-1405**

The undersigned declares that Patent Number 5,180,668 covers the drug substance lepirudin and its therapeutic use as an anticoagulant.

The drug product Refludan, containing the active substance lepirudin, is subject of this application for which approval is being sought.

The applicant Behringwerke AG is a subsidiary of Hoechst AG, Frankfurt/Main, Germany.

Brock 12.16.91

Name / Date Title

Dr. Franz Xaver Brock Responsible Head (FDA related matters)

EXCLUSIVITY SUMMARY for NDA # 20-807 **SUPPL #** _____

Trade Name Refludan® **Generic Name** lepirudin (r-DNA) for Injection
Applicant Name Hoechst Marion Roussel **HFD-** 180

Approval Date _____

APPEARS THIS WAY ON ORIGINAL

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

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

   APPEARS THIS WAY ON ORIGINAL

   b) Is it an effectiveness supplement?

   YES /___/ NO /_X__/

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

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

   YES /_X__/ NO /___/

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

   _____

   _____

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

_____

_____

APPEARS THIS WAY ON ORIGINAL

Form OGD-011347 Revised 8/7/95; edited 8/8/95
cc: Original NDA Division File HFD-85 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /___/ NO /_X__/

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

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?

YES /___/ NO /_X__/

If yes, NDA # _____ Drug Name_____

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ON ORIGINAL

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

APPEARS THIS WAY
ON ORIGINAL

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

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

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ON ORIGINAL

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

1. Single active ingredient product.

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

YES /___/ NO /_X__/

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

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

APPEARS THIS WAY
ON ORIGINAL

2. Combination product.

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

YES /___/ NO /___/

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

NDA # _____ _____

NDA # _____ _____

NDA # _____ _____

APPEARS THIS WAY
ON ORIGINAL

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

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

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

YES /___/ NO /___/

APPEARS THIS WAY
ON ORIGINAL

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

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

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

YES /___/ NO /___/

APPEARS THIS WAY
ON ORIGINAL

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:**

_____

_____

APPEARS THIS WAY
ON ORIGINAL

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

YES /___/ NO /___/

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

YES /___/ NO /___/

APPEARS THIS WAY
ON ORIGINAL

If yes, explain: _____

_____

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

YES /___/ NO /___/

APPEARS THIS WAY
ON ORIGINAL

If yes, explain: _____

_____

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

Investigation #1, Study # _____

Investigation #2, Study # _____

Investigation #3, Study # _____

APPEARS THIS WAY
ON ORIGINAL

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

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

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

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

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

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

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

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

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

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

Investigation #_, Study # _____

Investigation #_, Study # _____

Investigation #_, Study # _____

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

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

Investigation #1

IND # ____ YES /___/ NO /___/ Explain: _____

_____

Investigation #2

IND # ____ YES /___/ NO /___/ Explain: _____

_____

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

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2 !

YES /___/ Explain _____ ! NO /___/ Explain _____

_____ ! _____

_____ ! _____

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

YES /___/ NO /___/

If yes, explain: _____

_____

_____

_____

/S/

Signature 2/27/98 Date

Title: Regulatory Health Project Manager

APPEARS THIS WAY ON ORIGINAL

/S/

Signature of Division Director 2-28-98 Date

APPEARS THIS WAY ON ORIGINAL

cc: Original NDA Division File HFD-85 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action.

NDA/PLA/PMA # NDA 20-807 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HFD-180 Trade and generic names/dosage form: Refludan [lepirudin (rDNA) for Injection] Action: (AP) AE NA

Applicant Hoechst Marion Roussel Therapeutic Class 1P

Indication(s) previously approved N/A

Pediatric information in labeling of approved indication(s) is adequate X inadequate __

Proposed indication in this application HIT and associated thromboembolic disease in order to prevent further thromboembolic complications

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___Yes (Continue with questions) X No (Sign and return the form)

WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

__Neonates (Birth-1month) __Infants (1month-2yrs) __Children (2-12yrs) __Adolecents(12-16yrs)

__1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

__2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

__3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

- __a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.
- __b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.
- __c. The applicant has committed to doing such studies as will be required.
  - ___ (1) Studies are ongoing,
  - ___ (2) Protocols were submitted and approved.
  - ___ (3) Protocols were submitted and are under review.
  - ___ (4) If no protocol has been submitted, attach memo describing status of discussions.
- __d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

__4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

__5. **PEDIATRIC LABELING MAY NOT BE ADEQUATE.**

- __a. Pediatric studies are needed.
- __b. Pediatric studies may not be needed but a pediatric supplement is needed.

APPEARS THIS WAY ON ORIGINAL

X 6. If none of the above apply, attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE IV COMMITMENTS IN THE ACTION LETTER? ___Yes X No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

/S/

Signature of Preparer and Title Regulatory Health Project Manager

2/27/98

Date

APPEARS THIS WAY ON ORIGINAL

cc: Orig NDA/PLA/PMA # NDA 20-807
HFD-180/Div File
NDA/PLA Action Package
HFD-006/ KRoberts (include labeling for all NME approvals;either draft or final)

(revised 9/15/97)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, KHYATI ROBERTS, HFD-6 (ROBERTSK)

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

NDA/PLA/PMA # NDA 20-807 Supplement # _____ Circle one: SE1 SE2 SE3 SE4 SE5 SE6

HF -180 Trade and generic names/dosage form: Refludan [lepirudin (rDNA) for Injection] Action: AP (AE) NA

Applicant Hoechst Marion Roussel Therapeutic Class 1P

Indication(s) previously approved N/A

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ___

Indication in this application HAT Type II and thromboembolic disease (For supplements, answer the following questions in relation to the proposed indication.)

___ 1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___ 2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___ 3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___ a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___ b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___ c. The applicant has committed to doing such studies as will be required.
___ (1) Studies are ongoing,
___ (2) Protocols were submitted and approved.
___ (3) Protocols were submitted and are under review.
___ (4) If no protocol has been submitted, attach memo describing status of discussions.

APPEARS THIS WAY ON ORIGINAL

___ d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

___ 4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

X 5. **If none of the above apply,** attach an explanation, as necessary. See page 2 of this form.

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

/S/ Project Manager 9/4/97

Signature of Preparer and Title Date

cc: Orig NDA/PLA/PMA #_____
HF_____/Div File
NDA/PLA Action Package
HFD-006/ SOlmstead (plus, for CDER/CBER APs and AEs, copy of action letter and labeling)

APPEARS THIS WAY ON ORIGINAL

NOTE: A new Pediatric Page must be completed at the time of each action even though one was prepared at the time of the last action. (revised 3/12/97)

December 31, 1996

DEBARMENT CERTIFICATION

We certify that to the best of our knowledge, neither Behringwerke AG, ClinTrials Research, Inc. nor their employees or affiliated persons associated with the development and submission of this New Drug Application have been convicted of any crime described in section 306, subsections (a) and (b) of the Generic Drug Enforcement Act of 1992. Behringwerke AG and ClinTrials Research, Inc. certifies that it does not and will not knowingly use, in any capacity, the services of any person or firm debarred under section 306, subsections (a) and (b) of the Generic Drug Enforcement Act of 1992.

Reiner Laske, Ph.D.
Drug Regulatory Affairs
Behringwerke AG
Marburg, FRG

B. Randall Vestal
Sr. Director, Strategic Regulatory Affairs
ClinTrials Research, Inc.
Research Triangle Park, NC 27709

MEMORANDUM

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

DATE: August 19, 1997

FROM: Acting Director, Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Approvable Action for Refludin, NDA 20-807

TO: Acting Director, Office of Drug Evaluation III, HFD 103

Heparin-associated thrombocytopenia (HAT-II) is a potentially serious complication of heparin therapy occurring in approximately 5% of patients exposed to this drug for few days or longer. The clinical relevance of HAT-II is related to its frequency, to the widespread use of heparin and heparin derivatives, and most of all, to its potentially catastrophic consequences. Simply discontinuing heparin in patients with HAT-II does not prevent the occurrence of new arterial or venous thromboembolic complications (TECs) which can lead to limb gangrene and need for amputation in 10-20% of patients or can result in death in 20-30% of patients.

Patients with HAT-II presenting with isolated thrombocytopenia are also at high risk of TECs. As shown recently in a 14 year study of HAT-II, the incidence of TECs in patients with isolated thrombocytopenia approaches 50% over the 10 to 30 days after discontinuation of heparin. In this study, the mortality rate was approximately 20% for both HAT-II groups with or without thrombosis.

At present time there is no alternative anticoagulant regimen to replace heparin in HAT-II patients presenting with thrombosis or in need of thromboprophylaxis because the Low Molecular Weight Heparins (LMWH) cross-react with anti-heparin antibodies and warfarin does not provide immediate anticoagulation.

The efficacy and safety of a recombinant hirudin (HBW 023) in patients with confirmed heparin-associated thrombocytopenia have been assessed in two prospective, multicenter Phase III clinical trials.
Due to ethical considerations and lack of available comparator, the two studies were planned as prospective, open-label,

uncontrolled trials whose primary objective was to demonstrate that iv. treatment with HBW 023 provided effective anticoagulation (as indicated by APTT determinations), without continuation of the underlying immunological process (as indicated by recovery of platelet counts).
As secondary objectives, the combined and individual incidences of arterial or venous thromboembolic complications (TECs), limb amputations, and deaths were analyzed (secondary endpoint).

At a pre-NDA meeting held on 4-11-1996 with FDA representatives, the Agency pointed out the limitations of surrogate endpoints for primary efficacy and the need to establish the efficacy and safety of HBW 023 on the clinical events rather than on surrogate endpoints of platelet count and aPTT values. Therefore, the Agency recommended that the clinical events (death, amputation and new TECs) in the study population treated with HBW 023 be compared with an historical control of patients with HAT-II untreated or treated with any non-approved treatments. The Agency also recommended to focus on the patients with HAT-II and thrombosis for the comparison of clinical events; namely, to compare the clinical events occurring in patients presenting with thrombosis in the prospective study to the historical control consisting of 91 patients with HAT-II and documented thrombosis at the time of laboratory diagnosis.

The two clinical trials were performed in Germany from March 1994 to April 1996. Both studies had Dr. Greinacher as principal investigator, however, because of the relative rarity of HAT-II, the total patient population of 198 patients in the two studies was enrolled by several investigators at numerous centers from multiple geographical locations. The studies were acceptable since there is no evidence that the patient population or the diagnosis and management of HAT-II in Germany differs from the US.

A total of 82 patients were enrolled in study B7 and 116 patients in study NR13. In both studies, 4 groups of patients were treated with HBW 023: A1= Patients with HAT-II and thrombosis not receiving thrombolytics; Group A2= Patients with HAT-II and thrombosis receiving thrombolytics; Group B= Prophylaxis of venous or arterial thromboembolism; Group C= Anticoagulation during cardiopulmonary bypass (CPB). Only the patients in groups A1 and A2 were compared to the historical control for incidence of clinical events.

In both studies, patients requiring prolonged anticoagulation were gradually switched to oral anticoagulant therapy and

discontinued from HBW 023 when adequate PT or INR were achieved. The oral anticoagulant most frequently used in the studies was phenprocoumon (Marcumar). This vit. K-inhibitor is not used in United States where warfarin is the most widely used oral anticoagulant. The two compounds have different pharmacokinetics, however, as attested by an independent expert (Dr. J Hirsh, Director, Hamilton Civic Hospital Research Center, Hamilton, Ontario), both are coumarin derivatives with identical mechanism of action of impairing vit.K-dependent clotting factors, both are used for the same indications, and both are monitored by the PT using the same targeted INR.

With regard to the primary efficacy criteria, the overall response rate in terms of platelet recovery or maintenance alone was 91.8% in study B7 and 86.1% in study NR13. Effective anticoagulation was achieved in 73.5% and 77.2% of patients in study B7 and NR13 respectively. The total proportion of responders for the combined response of anticoagulation and platelet recovery was significantly greater (>65%) than the pre-specified limit of 20% (>65%, $p<0.0001$) in both prospective studies.

It must be noted, however, that platelet counts in patients with heparin-induced thrombocytopenia usually recover spontaneously, provided that heparin is no longer administered. No direct effect of HBW 023 on speed or extent of platelet recovery was expected, nor found. The time course of platelet counts during the study, in fact, clearly shows that the platelet recovery had already began before treatment with HBW 023 was initiated. The results of the primary efficacy are relevant, however, because they indicate that adequate anticoagulation can be provided by HBW 023 in patients with anti-heparin antibodies without continuation of the underlying immunologic process.

With regard to the efficacy of HBW 023 for prevention of clinical events of new TECs, limb amputation or death, the study patients presenting with thrombosis were compared to the historical control for incidence of clinical events. Since no definite starting point of therapy could be determined for the historical control, the date of laboratory confirmation of HAT-II diagnosis was considered to be the most appropriate starting point for comparing the clinical results. To account for differences in length of observation periods, time-to-event analyses were performed. A maximum period of observation of 60 days from laboratory confirmation of HAT-II was defined.

The two studies were discordant in regard to clinical efficacy

endpoints. In **study B7**, the cumulative incidence of combined events since HAT confirmation in 54 study patients, compared with that reported in the historical control of 91 patients, revealed a statistically significant difference in favor of the HBW 023-treated group (20.4% versus 42.9% four weeks after HAT confirmation, p=0.0142, log-rank test). The observed difference in the combined endpoint in favor of the HBW 023 group was mainly due to the reduction of the incidences of new TECs (p=0.0786). The unadjusted hazard ratio (HBW 023: historical control) was 0.443 (95% CI 0.225-0.871): the adjusted hazard ratio was 0.439 (95% CI 0.2

In **study NR13**, the overall mortality of 9.5%; causes of death were attributed to the severity of the underlying disease, and none was considered to be related to the study drug. Twelve patients (10.3%) experienced a new TEC, eleven of these during HBW 023 treatment. Nine patients (7.8%) underwent limb amputation during the study period. The incidence of the combined clinical endpoint (death, limb amputation or new TEC) was 22.4% during the entire study period.
However, no statistically significant differences between HBW 023-treated group and historical control were seen for the combined and individual incidence of death, limb amputations, and new TECs.

In both prospective studies, initiation of therapy was delayed by a mean of 1.5 days from the time of laboratory confirmation of HAT-II diagnosis. Consequently, the treatment effect of HBW 023 on clinical endpoint was diminished by events occurring before the start of treatment. This finding had not been anticipated when the time of laboratory confirmation of HAT-II was selected as starting point for observation. Since no therapeutic effect of HBW 023 could be expected prior to its initiation, an exploratory analysis was performed to compare the incidence of the combined endpoint occurring from the start of HBW 023 treatment in the prospective studies to that occurring after the selection of first treatment following HAT confirmation in the historical control. This analysis appears to be clinically valid, moreover, it emphasized the need for early antithrombotic treatment when the risk of TECs appears to be greatest and it also allows to compare HBW 023 treatment with the different treatments used in the historical control group.

In both studies, in fact, the average combined event rate per patient day during HBW 023 treatment was reduced compared to the period between laboratory confirmation of HAT-II and end of treatment.

In **study B7,** the incidence of any event in the combined clinical endpoint from start of therapy was 13% in the patients compared to 40.3% in the historical control (p=0.0004). The estimated adjusted hazard ratio (HBW 023: historical control) was 0.205 indicating a RR of clinical events of 80%. When HBW 023 was compared to other regimens used as first selected treatment, the risk of combined endpoints was significantly lower in the HBW 023 group compared to HAT patients treated with heparinoid (p=0.0004) or with oral anticoagulation (phenprocoumon) (p=0.0125).
In **study NR13,** the incidence of the combined endpoints (death, amputation, or new TEC) from start of therapy was numerically lower in the HBW 023 group than in the historical control group (17.9% versus 21.3% by Day 7, 33.3% versus 40.3% by Day 28); however, the difference was not statistically significant (p= 0.66). No statistically significant difference in incidence of clinical events was noted between the HBW 023 group and the individual historical first selected treatments.

The following imbalances were noted among patient populations that may have influenced the clinical outcomes in the two studies:
- Event occurring on the day of laboratory diagnosis of HAT-II (start of observation period) were not included in the historical control; this resulted in an underestimation of events in the control group.
- Severe thromboembolic events, such as pelvic and iliac vein thrombosis, vena cava thrombosis, and arterial thromboembolism, occurring during heparin therapy were more frequent in patients enrolled in study NR13 compared to historical control.
- More patients in study NR13 than in study B7 had multiple TECs: 53% of the patients with thrombosis had more 2 or more TECs in study B7, compared to 70% in study NR13.
- More than 35% of the patients excluded from enrollment in the two prospective studies (B7 and NR13) were patients with HAT-II and ongoing thrombosis who did not require parenteral anticoagulant therapy. This exclusion criterion was not applied to the historical control. Consequently, some patients with less severe prognosis may have been included in the historical control and excluded from the prospective studies population.

In the **pooled population** from the two studies, the cumulative incidence of the combined endpoint of new TECs, limb amputations or death occurring from the time of start of therapy was consistently lower in the population treated with HBW 023 compared to the historical control. The log-rank test showed a significant difference in favor of HBW 023 (p=0.004). Cumulative

incidences of new TECs showed statistically significant difference (p=0.005). Numerical differences not statistically significant were observed for amputation or death, however the incidence rate of death at 35 days was 8.9% in the HBW 023 group compared to 17.6% in the historical control.

Analyses of the patients enrolled in the other study groups of HAT-II patients (patients with thrombocytopenia without thrombosis of group B and patients undergoing CPB surgery in group C) were not performed because the patients were too few for meaningful analyses and because of lack of control group for comparison.
It was anticipated that patients with HAT-II presenting with isolated thrombocytopenia without ongoing thrombosis (group B) were at lower risk of TECs, and that a lower dose of HBW 023 would be effective for thromboprophylaxis. It is of note, however, that contrary to expectations, the combined event rate in the pooled group B was as high as 28%. Therefore, it appears that the risk for TECs persists in all HAT-II patients for a time despite discontinuation of heparin.
These observations have also been reported in the literature.

A significantly higher rate of documented bleeding events was observed in the prospective study population compared to the historical control. Bleeding of any severity occurred in 30% of patients in study B7, 42% in study NR13 (36% in the combined HBW 023-treated population), and in 15% in the historical control. The majority of bleeds in the HBW 023 group occurred as peri- or post-operative complication or hemorrhage at a disturbed site.

The overall incidence of major bleeding in the treated population was 16% (13% in study B7 and 18% in study NR13) compared to 7% in the historical control (p=0.008). It must be noted that patients in the prospective studies, contrary to the historical control, were at high risk of bleeding due to multiple antithrombotic therapy, i.e. HBW 023 plus oral anticoagulant, thrombolytics or antiplatelet agents.

No intracerebral (IC) hemorrhage occurred during the study, and none of the observed major bleeding events was fatal. However, the number of patient is small for meaningful assessment of events such as IC bleeding.

Two patients in study B7 and 6 patients in study NR13 (4% overall) experienced an allergic reaction during the study

period. In none of the three patients, HBW 023 treatment had to be discontinued due to the event.

A total of 38 patients (46%) in study B7 and 49 patients (42.2%) in study NR13 developed IgG antibodies against hirudin, including the three patients who had experienced an allergic reaction. None of the patients developed IgE antibodies. The first positive antibody values were observed four to six days after start of study treatment. Positive antibody testing persisted at 3 to 10 months after exposure.
The formation of antibodies against hirudin was not associated with reduced hirudin plasma levels or occurrence of clinical events, such as death, new TEC, major bleeding, or allergic/anaphylactic reaction. However, in 5 patients with anti-hirudin antibodies, the HBW 023 maintenance dose had to be reduced by 2-3-fold to maintain a stable aPTT, suggesting that anti-hirudin antibodies may enhance the anticoagulant effect of r-hirudin.
Five patients with persisting anti-hirudin antibodies were re-exposed to HBW 023 during a repeated treatment course, none of them experienced any allergic reaction.

On March 13, 1997, the European Commission issued a Marketing Authorization for HBW 023 (Refludan) for the treatment of adult patients with heparin-associated thrombocytopenia (HAT-II) and thromboembolic disease mandating parenteral antithrombotic therapy.

The overall assessment of risk/benefit ratio indicates that treatment with HBW 023 reduced the incidence of the clinical endpoint of death by 9%, limb amputation by 4%, new TECs by 17%. The incidence of the combined endpoint was reduced by 27%. Bleeding complications were increased by the administration of HBW 023: the incidence of any bleeding was increased by 18% and the incidence of bleeding requiring transfusion was increased by 12%.

Based on the results of two studies, it is recommended that HBW 023 (Refludan, Lepirudin) for the treatment of patients with HAT-II presenting with thromboembolic complications be approvable, pending the issues listed in the regulatory recommendations of the medical review, to be addressed by the sponsor.

The recommended initial dose regimen of HBW 023 is 0.4 mg/kg bw iv bolus followed by 0.15 mg/kg bw/hr as a continuous infusion

for 2 to 10 days or longer if clinically indicated. Dosage is monitored by aPTT and adjusted as needed to maintain the aPTT at 1.5 to 3.0 times control. In patients scheduled to receive oral anticoagulation with coumarin derivatives after HBW 023 therapy, HBW dosage is reduced to aPTT of just above 1,5 times control before starting oral anticoagulation. HBW 023 is discontinue when the INR of 2.0 is reached.

We hope you will concur with our approvable recommendation. We would be glad to meet with you to discuss any question you may have

/S/

Lilia Talarico, M.D.

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cc:
NDA 20-807
HFD-180
HFD-180/LTalarico
HFD-181/CSO
HFD-180/JChoudary
HFD-180/EDuffy
f/t 8/18/97 jgw
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MEMORANDUM

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

DATE: January 23, 1998

FROM: Director, Division of Gastrointestinal and Coagulation Drug Products, HFD 180

SUBJECT: Information Amendment
Response to Approvable Letter
Safety Update

TO: NDA 20-807

THROUGH: Acting Director, Office of Drug Evaluation III
HFD 103

BACKGROUND

NDA 20-807 for Refludan was submitted by Behringwerke AG on December 31, 1996. Refludan is a r-hirudin indicated for anticoagulation in patients with Heparin-Associated Thrombocytopenia type II (HAT-II) and associated thromboembolic disease to prevent further thromboembolic complication.

An approvable letter was issued on 9-8-1997 with request for submission of additional CMC and microbiology information, Safety Update, and revised package insert and with request for postmarketing commitments for additional studies of Refludan in patients with HAT-II without thrombotic complications and in patients with latent HAT-II.

On 11-21-1997, the sponsor responded to the Approvable letter with the submission of a draft annotated package insert, the Safety Update, the first periodic report on the European Drug Monitoring Program, safety data from the ongoing study OASIS-2 for cardiac indications (statement by the DSMB), responses to the post-approval commitments requested by the Agency including comments on pediatric indication, and responses to biopharmacology and chemistry issues of stability testing schedule.

This review will address only the following clinical issues:

- Safety Update
- Periodic Report on the EDMP
- Sponsor's response for post-approval commitment
- Use in the Pediatric Population
- Professional Labeling

1.0 SAFETY UPDATE

This safety update is collected according to the format of the Integrated Summary of Safety included in the NDA submission (NDA Section 8.IX).

The *Safety Update* (SU) is comprised of all subjects enrolled in 24 clinical pharmacology studies and 22 clinical studies as of July 18, 1997. The SU include data from six Pharmacology studies, including four

studies performed in Japan, that were ongoing at the time of the ISS; data from the two controlled clinical trials of the NDA (B7, NR13), other completed controlled clinical trials, including two studies performed in Japan (BI-B6, NR2, NR6, NR11, NR12, NR19, NR20, NR22, NR24), other completed uncontrolled clinical trials (NR1, NR3-NR5), and ongoing clinical studies (NR21, NR23).

1.1 METHODS OF ANALYSIS

Identical definitions of Adverse Event (AE), Serious Adverse Event (SAE) were used in the SU as compared to the ISS.

The length of observation periods for adverse events varied in the individual studies. Usually, the observation period in clinical trials was defined from the start of study treatment until 14 days after the end of study treatment, except for the clinical pharmacology studies, where the observation period ended 24 hours after the last dose. Documented adverse events that occurred more than 14 days after the end of study treatment were listed separately.

The investigators were asked to report diagnoses where possible, together with associated symptoms. If a diagnosis could not be made, the observed symptoms were reported as adverse events. Symptoms associated with a diagnosis were not considered in the frequency tables.

The causality of each adverse event was classified by the investigator as either not related or possibly related to the study drug.

The definition of major bleedings was provided in each study protocol, however the definition was not the same across the individual studies. In order to compare the incidence of major bleedings across all clinical studies, a common definition of major bleedings was established for the ISS/US, discriminating between overt and non-overt bleedings:

An overt bleeding was defined as major
- if it required the transfusion of at least two units of blood or
- if it required a surgical intervention or
- if it was a serious adverse event.

A non-overt bleeding was defined as major
- if it was an intracranial bleeding or
- if it required the transfusion of at least two units of blood and if a drop in hemoglobin of at least 2 g/l was observed between the start of study treatment and the first transfusion.

Using the above definition, 12 patients were reclassified as having major bleeding in the SU and were included in the adverse event summary tables. Conversely, 23 patients who had a major bleeding according to the original study reports based on an isolated drop in hemoglobin (21 cases), transfusion of only one unit of blood (1 case), or late bleeding (1 case), were reclassified as patients without major bleeding in the SU.

Two different definitions of type I allergic reactions were applied. The first definition referred to the allergic, anaphylactic and anaphylactoid reactions reported as such by the investigators. In the second definition, in addition, symptoms possibly indicating an allergic reaction were

considered (i.e., angioedema, bronchospasm, chills, cough, dyspnea, face edema, hot flashes, larynx edema, maculopapular rash, pruritus, rash, stridor, tongue edema, and urticaria).
Type III allergic reactions were screened by monitoring the following events: arthralgia, arthritis, Guillain Barre' syndrome, immune system disorder, joint disorder, neuritis, proteinuria, serum sickness and vasculitis.

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1.2. TABLE OF STUDIES

Overall, 323 subjects participated in 24 controlled and uncontrolled clinical pharmacology studies.

The historically controlled clinical trials B7 and NR13 in which 198 patients were treated with lepirudin (NDA pivotal studies) are shown in Table 3.3. The ongoing uncontrolled clinical trial for HAT-II (NR21), shown in Table 3.4.b., has enrolled 207 patients treated with lepirudin as of July 18,1997. No other uncontrolled clinical trials were ongoing as of July 18, 1997. Other controlled clinical trials comprising 14 clinical studies for 5 indications of 1908 patients are shown in Table 3.5. One controlled clinical trial ongoing (NR23) is shown in Table 3.6. The total number of patients enrolled in this study and treated with lepirudin or heparin as of July 18, 1997 was 4010. Other uncontrolled are shown in Table 3.7.

Table 3.3: Controlled clinical trials - Historically controlled

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Serial No.	BW Study No.	Study dates	Design	HBW 023 Dosage Bolus (mg/kg)	HBW 023 Dosage Infusion (mg/kg/h)	HBW 023 Dosage s.c. (mg/kg)	Planned duration of medication	Number of patients* HBW 023	Number of patients* Control
Treatment with HBW 023 in patients with heparin-associated thrombocytopenia type II									
B 7	7D--301WC	03/94 - 07/95	OP, HIST-C, M					82	-
NR13	7MN-301WC	07/95 - 04/96	OP, HIST-C, M					116	-
+ Historical control								-	91
TOTAL IN CONTROL GROUP									91
TOTAL RECEIVING HBW 023								198	

* Numbers refer to patients with at least one dose of study drug.

Table 3.4.b: Uncontrolled clinical trials (ongoing)

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Serial No.	BW Study No.	Study dates	Design	HBW 023 Dosage Bolus (mg/kg)	HBW 023 Dosage Infusion (mg/kg/h)	HBW 023 Dosage s.c. (mg/kg)	Planned duration of medication	Number of patients* HBW 023	Number of patients* Control
Treatment with HBW 023 in patients with heparin-associated thrombocytopenia type II									
NR21	7MN-302WC	04/96 - 05/97	OP, M					207	-
TOTAL RECEIVING HBW 023								207	-

* Numbers refer to patients with at least one dose of study drug.

Design: DB = double-blind; PB = partially blind; OP = open; DOSE-C = dose-controlled; HEP-C = heparin-controlled; PLA-C = placebo-controlled; HIST-C = historically-controlled; ROU-C = vs. vs i.v.; SOL-C = 3 different solvents; M = multicenter; U = unicenter; CO = crossover

Table 3.5: Other clinical trials - Controlled

Serial No.	BW Study No.	Study dates	Design	HBW 023 Dosage: Bolus (mg/kg)	HBW 023 Dosage: Infusion (mg/kg/h)	HBW 023 Dosage: s.c. (mg/kg)	Planned duration of medication	Number of patients*: HBW 023	Number of patients*: Heparin control
Treatment with HBW 023 in conjunction with thrombolysis after AMI									
B1	7MN-202MI	05/92 - 04/93	OP, DOSE-C, M			-	48 h	143	-
B2	7MN-203MI	11/93 - 02/95	OP, HEP-C, DOSE-C, M			-		202	64
B3	7MN-301MI	03/94 - 06/94	DB, HEP-C, M	0.4	0.15	-		145	149
NR11	7MN-302MI	04/95 - 12/96	DB, HEP-C, M	0.2	-	0.5		604	604
Treatment with HBW 023 in patients with acute coronary syndromes not receiving thrombolysis									
B4	7MN-201AP	02/93 - 09/93	OP, HEP-C, DOSE-C, M			-	48 h	40	21
B5	7CDN201UA (OASIS Ia)	07/94 - 05/96	PB, HEP-C, DOSE-C, M			-	72 h	346	251
NR22	7CDN201UA (OASIS Ib)	12/95 - 11/96	PB, HEP-C, DOSE-C, M			-	72 h	190	118
NR2	7MN-201UA	01/93 - 07/93	OP, DOSE-C, M			-	72 h	43	-
NR12	7USA301MI	06/95 - 11/95	DB, HEP-C, PLA-C,M	0.2	0.1	-		30	60 (30 Hep, 30 Pla)
Therapy and prophylaxis of deep venous thrombosis									
B6	7MN-201TH	09/92 - 03/94	OP, HEP-C, DOSE-C, M	-	-	(twice daily)		118	38
Treatment with HBW 023 in other indications									
NR6	7B--201EC	10/90 - 05/91	OP, DOSE-C, U		-	-	1 bolus	20	-
NR24	7D--201EC	08/96 - 12/96	OP, HEP-C, U	0.2	0.1	0.5	2 - 3 d	11	11
Completed studies in patients with DIC									
NR19	8J--201DK	07/93 - 03/94	OP, DOSE-C, M	-	0.005 - 0.01	-		6	-
NR20	8J--202DK	07/94 - 03/96	OP, DOSE-C, M	-	0.0025- 0.02	-	7 d	10	
TOTAL IN HEPARIN-CONTROLLED STUDIES									1316
TOTAL RECEIVING HBW 023								1908	

* Numbers refer to patients with at least one dose of study drug. In study B3, 3 patients randomized to HBW 023 and 5 patients randomized to Heparin control did not receive study drug. In study B2, 5 patients randomized to the HBW 023 group and 1 patient randomized to the Heparin group were not considered, in study B5 2 patients were each randomized to HBW 023 and heparin but did not receive and study medication and in study B6 2 patients randomized to HBW 023 and 2 patients randomized to Heparin were not considered for the same reason. In study NR11 one patient was randomized to Heparin but received HBW 023.

Design: DB = double-blind; PB = partially blind; OP = open; DOSE-C = dose-controlled; HEP-C = heparin-controlled; PLA-C = placebo-controlled; HIST-C = historically-controlled; ROU-C = ss. vs i.v.; SOL.-C = 3 different solvents; M = multicenter; U = unicenter; CO = crossover

Table 3.6: **Other clinical trials - Controlled (ongoing studies)**

Serial No.	BW Study No.	Study dates	Design	HBW 023 Dosage: Bolus (mg/kg)	HBW 023 Dosage: Infusion (mg/kg/h)	HBW 023 Dosage: s.c. (mg/kg)	Planned duration of medication	Number of patients*: HBW 023	Number of patients*: Heparin control	Number of patients*: blinded
Treatment with HBW 023 in patients with acute coronary syndromes not receiving thrombolysis										
NR23	7MN-302UA	08/96 ongoing	DB, HEP-C, M	0.4	0.15	-	72 h	-	-	4010
TOTAL IN HEPARIN-CONTROLLED STUDIES										4010

- Numbers refer to patients with at least one dose of study drug.

Table 3.7: **Other clinical trials - Uncontrolled**

Serial No.	BW Study No.	Study dates	Design	HBW 023 Dosage: Bolus (mg/kg)	HBW 023 Dosage: Infusion (mg/kg/h)	HBW 023 Dosage: s.c. (mg/kg)	Planned duration of medication	Number of patients*: HBW 023
Treatment with HBW 023 in conjunction with thrombolysis after AMI								
NR1	7MN-201MI	01/91 - 08/92	OP, M	0.07	0.05	-	48 h	40
Therapy and prophylaxis of DVT								
NR3	7ZA-201OS	07/91 - 02/92	OP, U	0.1	-	-	10 d	10
NR4	7F--201TH	03/91 - 10/91	OP, M	0.07	0.05	-	4 - 6 d	11
NR5	7F--202TH	12/91 - 04/92	OP, U	-	-	0.75	4 - 6 d	10
TOTAL RECEIVING HBW 023								71

- Numbers refer to patients with at least one dose of study drug.

Design: DB = double-blind; PB = partially blind; OP = open; DOSE-C = dose-controlled; HEP-C = heparin-controlled; PLA-C = placebo-controlled; HIST-C = historically-controlled; ROU-C = sc. vs i.v.; SOL-C = 3 different solvents; M = multicenter; U = unicenter; CO = crossover

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Table 3.9 shows the extent of exposure to the drug by gender.

Table 3.9: **Extent of exposure to HBW 023***

	male	female	Total
< 1 Day	233	60	293
1 Day - 2 Days	180	43	223
> 2 Day - 1 week	1272	485	1757
> 1 week	107	120	227
Total	1792	708	2500

* excluding studies NR21 and NR23

1.3. PRESENTATION OF DATA

Presentation of data in the SU is identical to that in the ISS. Columns showing the incidences of the ISS are headed "ISS" and columns showing the updated incidences of the SU are headed " UPD".

The main part of the SU is comprised of an overview of deaths, serious adverse events (SAE), adverse events (AE), and discontinuations of study medication due to adverse events by indication. The overview of AEs presents data according to body system and frequency. Separate tables provide possibly related AEs grouped by body system. The Hoechst Adverse Reaction Terminology System (HARTS) was used for coding AEs.

All patients who received at least one dose of study drug were included in the analysis of AEs. Patients who were randomized, but not treated, were excluded. Only adverse events occurring during or after lepirudin treatment are described in the SU. Patients were evaluated as treated.
For ongoing studies (NR21, NR23), July 18, 1997 was defined as cut-off date for the SU. For study NR21, AEs are not discussed in detail because the data collection is still ongoing, however, all deaths, SAEs and AEs leading to permanent discontinuation of study medication are summarized Tables 4.20-4.24b. For study NR23, only SAEs reported up to the cut-off date were incorporated. For the estimation of pooled incidences of these events, the number of patients at risk was estimated from the total number of patients randomized by the cut-off date.

1.4. ADVERSE EVENTS IN CLINICAL TRIALS

1.4.1 Overall summary of AEs

An overall summary of AEs reported in 2161 patients treated with lepirudin from completed clinical trials, excluding phase I and Japanese studies, is shown in Table 4.1. Of these 2161 patients, 85 patients died (3.9%), 343 patients experienced at least one SAE (15.9%), and in 185 patients (8.6%), lepirudin treatment was permanently discontinued due to an AE.

The overall incidence of major bleeding was 5.1% (Table 4.3). In indications other than HAT-II, the incidence was highest in patients with AMI undergoing thrombolysis (5.3%), while it was lower in patients with acute coronary syndromes without additional thrombolysis (1.4%) and in patients with deep venous thrombosis (3.4%).

In contrast, major bleeding events were reported in 18.2% of HAT-II patients (Table 4.3). These patients probably have a greater risk of bleeding due to thrombocytopenia, possibly activated coagulation and/or fibrinolysis system, possible consumption of clotting factors.

The overall incidence of minor bleeding was 21.4%. Individual incidences were 24.3% in patients with AMI undergoing thrombolysis, 16.9% in patients with acute coronary syndromes without additional thrombolysis, 13.4% in patients with deep venous thrombosis, and 28.8% in HAT-II patients (Table 4.4).

Integrated Summary of Safety (Update) - Lepirudin

Table 4.1: Summary of adverse events

(excluding non-fatal MI, angina pectoris and cardiogenic shock in studies 84, 85, MR2, MR12, M22).

All indications

	Study type									
	Control_ISS		Other_ISS		Total_ISS		Control_UPD		Other_UPD		Total_UPD	
	N	%	N	%	N	%	N	%	N	%	N	%
Patients treated	82	100.0%	948	100.0%	1030	100.0%	198	100.0%	1963	100.0%	2161	100.0%
Patients with adverse events (AE)	49	59.8%	515	54.3%	564	54.8%	126	63.6%	1101	56.1%	1227	56.8%
Patients with possibly related AEs	27	32.9%	314	33.1%	341	33.1%	71	35.9%	535	27.3%	606	28.0%
Patients with serious AEs	26	31.7%	121	12.8%	147	14.3%	71	35.9%	272	13.9%	343	15.9%
Patients with possibly related serious AEs	9	11.0%	52	5.5%	61	5.9%	28	14.1%	100	5.1%	128	5.9%
Patients who died due to AEs	6	7.3%	28	3.0%	34	3.3%	17	8.6%	68	3.5%	85	3.9%
Patients who died due to possibly related AEs	.		11	1.2%	11	1.1%	.		24	1.2%	24	1.1%
Study drug permanently discontinued due to AEs	8	9.8%	83	8.8%	91	8.8%	29	14.6%	156	7.9%	185	8.6%
Study drug permanently discontinued due to possibly related AEs	3	3.7%	62	6.5%	65	6.3%	11	5.6%	106	5.4%	117	5.4%
Patients with AEs that were serious or led to permanent discontinuation of study drug	27	32.9%	154	16.2%	181	17.6%	74	37.4%	328	16.7%	402	18.6%
Patients with possibly related AEs that were serious or led to perm. discont. of study drug	11	13.4%	86	9.1%	97	9.4%	31	15.7%	153	7.8%	184	8.5%

Integrated Summary of Safety (Update) - Lepirudin

Table 4.3: Incidence of major bleedings in patients treated with MBW 023

	Study type																	
	Control_ISS			Uncontr._ISS			Total_ISS			Control_UPD			Uncontr._UPD			Total_UPD		
Indication	No of pat. treated	No of pat. with event	%	No of pat. treated	No of pat. with event	%	No of pat. treated	No of pat. with event	%	No of pat. treated	No of pat. with event	%	No of pat. treated	No of pat. with event	%	No of pat. treated	No of pat. with event	%
NAT type II	82	15	18.3	.	.	.	82	15	18.3	198	36	18.2	.	.	.	198	36	18.2
AMI with thrombolysis	490	35	7.1	40	2	5.0	530	37	7.0	1094	58	5.3	40	2	5.0	1134	60	5.3
Acute coronary syndromes without thrombolysis	249	3	1.2	.	.	.	249	3	1.2	649	9	1.4	.	.	.	649	9	1.4
Deep venous thrombosis	118	1	0.8	31	4	12.9	149	5	3.4	118	1	0.8	31	4	12.9	149	5	3.4
Other indications - Hemodialysis	20	0	0.0	.	.	.	20	0	0.0	20	0	0.0	.	.	.	20	0	0.0
Other indications - CPB	.	.	.	.	.	.	.	.	.	11	1	9.1	.	.	.	11	1	9.1
Total (*)	959	54	5.6	71	6	8.5	1030	60	5.8	2090	105	5.0	71	6	8.5	2161	111	5.1

Integrated Summary of Safety (Update) - Lepirudin

Table 4.4: Incidence of minor bleedings in patients treated with MBW 023

	Study type																	
	Control_ISS			Uncontr._ISS			Total_ISS			Control_UPD			Uncontr._UPD			Total_UPD		
Indication	No of pat. treated	No of pat. with event	%	No of pat. treated	No of pat. with event	%	No of pat. treated	No of pat. with event	%	No of pat. treated	No of pat. with event	%	No of pat. treated	No of pat. with event	%	No of pat. treated	No of pat. with event	%
NAT type II	82	18	22.0	.	.	.	82	18	22.0	198	57	28.8	.	.	.	198	57	28.8
AMI with thrombolysis	490	178	36.3	40	8	20.0	530	186	35.1	1094	267	24.4	40	8	20.0	1134	275	24.3
Acute coronary syndromes without thrombolysis	249	33	13.3	.	.	.	249	33	13.3	649	110	16.9	.	.	.	649	110	16.9
Deep venous thrombosis	118	18	15.3	31	2	6.5	149	20	13.4	118	18	15.3	31	2	6.5	149	20	13.4
Indications - Hemodialysis	20	0	0.0	.	.	.	20	0	0.0	20	0	0.0	.	.	.	20	0	0.0
Other indications - CPB	.	.	.	.	.	.	.	.	.	11	0	0.0	.	.	.	11	0	0.0
Total (*)	959	247	25.8	71	10	14.1	1030	257	25.0	2090	452	21.6	71	10	14.1	2161	462	21.4

(*) excluding phase I and Japanese studies

Four single cases of kidney failure (0.2%) were reported in the different studies with no evidence of causal relationship with lepirudin treatment.

Allergic, anaphylactic or anaphylactoid reactions as coded in the study reports were reported in a total of 38 lepirudin patients (1.8%). In 25 patients (1.2%), these reactions were considered to be possibly related to treatment with lepirudin (Tables 4.5a and 4.5b). "Possible allergic reactions" were reported in a total of 48 lepirudin patients (2.2%). In 13 patients (0.6%), these reactions were considered to be possibly related to treatment with lepirudin (Tables 4.6a and 4.6b). Forty six (53.5%) of all 86 lepirudin patients who suffered allergic, anaphylactic, anaphylactoid or possible allergic reactions received concomitant thrombolytic therapy and/or contrast media for coronary angiography.

Table 4.5.a: Incidence of allergic reactions in patients treated with HMR 023 (coded as allergic reaction, anaphylactic reaction or anaphylactoid reaction)

	Study type																	
	Control_ISS			Uncontr._ISS			Total_ISS			Control_UPD			Uncontr._UPD			Total_UPD		
Indication	No of pat. treated	No of pat. with event	%	No of pat. treated	No of pat. with event	%	No of pat. treated	No of pat. with event	%	No of pat. treated	No of pat. with event	%	No of pat. treated	No of pat. with event	%	No of pat. treated	No of pat. with event	%
MAT type II	82	2	2.44	.	.	.	82	2	2.44	198	2	1.01	.	.	.	198	2	1.01
AMI with thrombolysis	490	11	2.24	40	1	2.50	530	12	2.26	1094	33	3.02	40	1	2.50	1134	34	3.00
Acute coronary syndromes without thrombolysis	249	0	0.00	.	.	.	249	0	0.00	649	2	0.31	.	.	.	649	2	0.31
Deep venous thrombosis	118	0	0.00	31	0	0.00	149	0	0.00	118	0	0.00	31	0	0.00	149	0	0.00
Other indications - Hemodialysis	20	0	0.00	.	.	.	20	0	0.00	20	0	0.00	.	.	.	20	0	0.00
Other indications - CPB	.	.	.	.	.	.	.	.	.	11	0	0.00	.	.	.	11	0	0.00
Total (*)	959	13	1.36	71	1	1.41	1030	14	1.36	2090	37	1.77	71	1	1.41	2161	38	1.76

(*) excluding phase I and Japanese studies

Table 4.5.b: Incidence of possibly related allergic reactions in patients treated with HMR 023 (coded as allergic reaction, anaphylactic reaction or anaphylactoid reaction)

	Study type																	
	Control_ISS			Uncontr._ISS			Total_ISS			Control_UPD			Uncontr._UPD			Total_UPD		
Indication	No of pat. treated	No of pat. with event	%	No of pat. treated	No of pat. with event	%	No of pat. treated	No of pat. with event	%	No of pat. treated	No of pat. with event	%	No of pat. treated	No of pat. with event	%	No of pat. treated	No of pat. with event	%
MAT type II	82	2	2.44	.	.	.	82	2	2.44	198	2	1.01	.	.	.	198	2	1.01
AMI with thrombolysis	490	5	1.02	40	0	0.00	530	5	0.94	1094	23	2.10	40	0	0.00	1134	23	2.03
Acute coronary syndromes without thrombolysis	249	0	0.00	.	.	.	249	0	0.00	649	0	0.00	.	.	.	649	0	0.00
Deep venous thrombosis	118	0	0.00	31	0	0.00	149	0	0.00	118	0	0.00	31	0	0.00	149	0	0.00
Other indications - Hemodialysis	20	0	0.00	.	.	.	20	0	0.00	20	0	0.00	.	.	.	20	0	0.00
Other indications - CPB	.	.	.	.	.	.	.	.	.	11	0	0.00	.	.	.	11	0	0.00
Total (*)	959	7	0.73	71	0	0.00	1030	7	0.68	2090	25	1.20	71	0	0.00	2161	25	1.16

(*) excluding phase I and Japanese studies

Integrated Summary of Safety (Update) - Lepirudin

Table 4.6.a: Incidence of allergic reactions in patients treated with HBW 023 (possible allergic reactions, see footnote)

Indication	Study type: Control_ISS No of pat. treated	Control_ISS No of pat. with event	Control_ISS %	Uncontr._ISS No of pat. treated	Uncontr._ISS No of pat. with event	Uncontr._ISS %	Total_ISS No of pat. treated	Total_ISS No of pat. with event	Total_ISS %	Control_UPD No of pat. treated	Control_UPD No of pat. with event	Control_UPD %	Uncontr._UPD No of pat. treated	Uncontr._UPD No of pat. with event	Uncontr._UPD %	Total_UPD No of pat. treated	Total_UPD No of pat. with event	Total_UPD %
HAT type II	82	2	2.44	.	.	.	82	2	2.44	198	6	3.03	.	.	.	198	6	3.03
AMI with thrombolysis	490	17	3.47	40	2	5.00	530	19	3.58	1094	42	3.84	40	2	5.00	1134	44	3.88
Acute coronary syndromes without thrombolysis	269	7	2.81	.	.	.	269	7	2.81	649	36	5.55	.	.	.	649	36	5.55
Deep venous thrombosis	118	0	0.00	31	0	0.00	149	0	0.00	118	0	0.00	31	0	0.00	149	0	0.00
Other indications - Hemodialysis	20	0	0.00	.	.	.	20	0	0.00	20	0	0.00	.	.	.	20	0	0.00
Other indications - CPB	.	.	.	.	.	.	.	.	.	11	0	0.00	.	.	.	11	0	0.00
Total (*)	959	26	2.71	71	2	2.82	1030	28	2.72	2090	84	4.02	71	2	2.82	2161	86	3.98

(*) excluding phase I and Japanese studies

Included are events from the following list:

Allergic reaction, anaphylactic reaction, anaphylactoid reaction, angioedema, bronchospasm, isolated chills, isolated cough, isolated dyspnea, face edema, hot flashes, larynx edema, maculopapular rash, pruritus, rash, stridor, tongue edema, urticaria.

Integrated Summary of Safety (Update) - Lepiru...n

Table 4.6.b: Incidence of possibly related allergic reactions in patients treated with HBW 023 (possible allergic reactions, see footnote)

Indication	Study type: Control_ISS No of pat. treated	Control_ISS No of pat. with event	Control_ISS %	Uncontr._ISS No of pat. treated	Uncontr._ISS No of pat. with event	Uncontr._ISS %	Total_ISS No of pat. treated	Total_ISS No of pat. with event	Total_ISS %	Control_UPD No of pat. treated	Control_UPD No of pat. with event	Control_UPD %	Uncontr._UPD No of pat. treated	Uncontr._UPD No of pat. with event	Uncontr._UPD %	Total_UPD No of pat. treated	Total_UPD No of pat. with event	Total_UPD %
HAT type II	82	2	2.44	.	.	.	82	2	2.44	198	4	2.02	.	.	.	198	4	2.02
AMI with thrombolysis	490	11	2.24	40	0	0.00	530	11	2.08	1094	30	2.74	40	0	0.00	1134	30	2.65
Acute coronary syndromes without thrombolysis	269	2	0.80	.	.	.	269	2	0.80	649	4	0.62	.	.	.	649	4	0.62
Deep venous thrombosis	118	0	0.00	31	0	0.00	149	0	0.00	118	0	0.00	31	0	0.00	149	0	0.00
Other indications - Hemodialysis	20	0	0.00	.	.	.	20	0	0.00	20	0	0.00	.	.	.	20	0	0.00
Other indications - CPB	.	.	.	.	.	.	.	.	.	11	0	0.00	.	.	.	11	0	0.00
Total (*)	959	15	1.56	71	0	0.00	1030	15	1.44	2090	38	1.82	71	0	0.00	2161	38	1.76

(*) excluding phase I and Japanese studies

Included are events from the following list:

Allergic reaction, anaphylactic reaction, anaphylactoid reaction, angioedema, bronchospasm, isolated chills, isolated cough, isolated dyspnea, face edema, hot flashes, larynx edema, maculopapular rash, pruritus, rash, stridor, tongue edema, urticaria.

1.4.2 Safety experience in clinical pharmacology studies

No SAE occurred in the pharmacology studies. A total of 36 non-serious AEs occurred in 30 healthy subjects (15.3%) and in 2 subjects with kidney disease (11.8%); of these, 21 AEs were possibly related to treatment with lepirudin. The most common related AEs were mild injection site reactions after s.c. injection (11 cases) and mild gingival bleeding (3 cases). Others were bronchospasm, epistaxis, nausea. In one healthy subject, a prolonged aPTT was attributed to a pre-existing kallikrein deficiency.

Micro- or macro hematuria occurred in 16 healthy subjects (8.2%). No other relevant chemistry, hematology or urinalysis abnormalities were observed.

Anti-hirudin IgG antibodies not associated with allergic reactions were detected in 9 normal subjects.

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1.4.3 Safety experience in HAT type II patients

In two controlled pivotal trials B7 and NR13 studies, 198 HAT-II patients were treated with lepirudin and 91 HAT-II historical control patients received treatments other than lepirudin (e.g., danaparoid, phenprocoumon, low molecular weight heparin, no anticoagulation).
A third study (NR21) in 207 HAT-II patients was completed by July 1997. However, data processing is still ongoing.

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Adverse events in completed studies (B7 and NR13)

The AEs *in* studies B7 and NRI3 are summarized in the following table:

Summary of most frequent adverse events
Controlled studies B7/NR13

Patients with	Total	Possibly related
-AEs*	126(64%)	71(36%)
Hemorrhage	38(19%)	25(13%)
Decreased hemoglobin	17(9%)	2(1%)
Hematuria	13(7%)	4(5%)
Fever	12(6%)	5(3%)
Anemia	9(5%)	3(2%)
Injection site hemorrhage	9(5%)	6(3%)
-SAEs**	71(36%)	28(14%)
Hemorrhage	20(10%)	13(7%)
Pulmonary embolus	7(4%)	1(1%)
Hemothorax	6(3%)	4(2%)
Sepsis	6(3%)	0(0%)
Heart failure	4(2%)	0(0%)
Multi organ failure	4(2%)	0(0%)
-Fatal SAEs	17(9%)	0(0%)
Sepsis	6(3%)	0(0%)
Heart failure	4(2%)	0(0%)
Multi organ failure	4(2%)	0(0%
-Discontinuations due to AEs	29(15%)	11(6%)
Sepsis	5(3%)	0(0%)
Thrombotic Occlusion	4(2%)	0(0%)
Hemorrhage	3(2%)	3(2%)
Multi organ failure	3(2%)	0(0%)

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*including SAE; **including fatal SAEs

Bleeding Events: Major bleedings were reported in 36 (18%) patients (Table 4.3, page 7). Minor bleedings occurred in 57 (29%) patients (Table 4.4, page 7).

Allergic Reactions: Two patients (1.0%) experienced allergic reactions which were judged by the investigators to be possibly related to treatment with lepirudin (Tables 4.5a, 4.5b, page 8). Four patients (2.0%) experienced possible allergic reactions, two of which (1.0%) were judged by the investigators to be possibly related to treatment with lepirudin (Tables 4.6a, 4.6b, page 9).

1.4.4. Safety experience during or after treatment with lepirudin in conjunction with thrombolysis after acute myocardial infarction

Five studies (B1-B3, NR1 and NR11) were performed in patients with AMI undergoing thrombolysis with either rt-PA or streptokinase (SK). A total of 1134 patients were treated with lepirudin, and 817 patients were treated with heparin. The lepirudin patients received i.v. bolus injections of 0.07 to 0.4 mg/kg, followed by an infusion at doses of 0.05 to 0.15 mg/kg/h for 48 to 72 hours, or a s.c. application of 0.5 mg/kg b.i.d. for 5 to 7 days.

Adverse events: The most frequent adverse events in studies B1-B3, NR1, and NR11 are summarized below (NDA 20-807/SU, p.19).

Summary of most frequent adverse events

Patients with	Studies B1-B3, NR11 (N=1094)		Study NR1 (N=40)		Total (N=1134)	
	Total	Possibly related	Total	Possibly related	Total	Possibly related
- AEs*	617 (56%)	365 (33%)	31 (78%)	18 (45%)	648 (57%)	383 (34%)
Inj. site hemorrhage	216 (20%)	193 (18%)	7 (18%)	7 (18%)	223 (20%)	200 (18%)
Angina pectoris+	102 (9%)	11 (1%)	15 (38%)	6 (15%)	118 (10%)	17 (1%)
Ventr. tachycardia	77 (7%)	12 (1%)	3 (8%)	3 (8%)	80 (7%)	15 (1%)
Hemorrhage	57 (5%)	50 (5%)	0 (0%)	0 (0%)	57 (5%)	50 (4%)
- SAEs**	224 (21%)	89 (8%)	8 (20%)	3 (8%)	232 (21%)	92 (8%)
Angina pectoris+	43 (4%)	2 (0.2%)	1 (3%)	1 (3%)	44 (4%)	3 (0.3%)
Inj. site hemorrhage	29 (3%)	26 (2%)	0 (0%)	0 (0%)	29 (3%)	26 (2%)
Ventr. fibrillation	31 (3%)	7 (1%)	2 (5%)	0 (0%)	33 (3%)	7 (1%)
- fatal SAEs	60 (6%)	23 (2%)	1 (3%)	1 (3%)	61 (5%)	24 (2%)
Cardiogenic shock	13 (1%)	1 (0.1%)	0 (0%)	0 (0%)	13 (1%)	1 (0.1%)
Heart failure	11 (1%)	5 (1%)	0 (0%)	0 (0%)	11 (1%)	5 (0.4%)
- discontinuations due to AEs	128 (12%)	87 (8%)	1 (3%)	0 (0%)	129 (11%)	87 (8%)
Inj. site hemorrhage	40 (4%)	36 (3%)	0 (0%)	0 (0%)	40 (4%)	36 (3%)

* including SAEs
** including fatal SAEs
\+ angina pectoris includes recurrent angina pectoris

Bleeding Events: Seven cerebral hemorrhages (0.6%) were observed. Five of these events were reported in study B3 (lepirudin in conjunction with rt-PA). In fact, this phase III study was terminated prematurely due to the observed high incidence of cerebral hemorrhage.
Major bleedings occurred in 60 patients (5.3%), and minor bleedings were reported in 275 patients (24.3%) (Tables 4.3 and 4.4, p. 7).

Allergic Reactions: Allergic reactions occurred in 34 patients (3.0%); in 23 of them (2.0%), the events were judged to be possibly related to lepirudin (Tables 4.5a and 4.5b, p. 8). Possible allergic reactions occurred in 10 patients (0.9%), in 7 (0.6%), the events were judged to be possibly related to lepirudin (Tables 4.6a and 4.6b, p.9).

1.4.5. Safety experience during or after treatment with lepirudin in patients with acute coronary syndromes not receiving thrombolysis

Completed studies: A total of 649 patients with acute coronary syndrome were treated with lepirudin and 458 patients were treated with heparin in five studies (B4, B5, NR2, NR 12 and NR22). The lepirudin patients received i.v. bolus injections of 0.2 to 0.5 mg/kg, followed by an infusion at doses of 0.1 to 0.24 mg/kg/h for 48 to 72 hours.

Ongoing studies: A total of 4010 patients with UA or acute MI without ST elevation were enrolled in study NR23 as of July 18, 1997. The lepirudin dosing scheme was 0.4 mg/kg i.v. bolus, followed by an infusion of 0.15 mg/kg/h for 72 hours. As this study is ongoing, only SAEs are reported.

The most frequent AEs in studies B4, B5, NR2, NRI2 and NR22 are summarized in the table shown below (NDA 20-807, p. 21 of SU):

Summary of most frequent adverse events
(excluding non-fatal MI, cardiogenic shock, angina pectoris, chest pain)

	Studies B4, B5, NR2, NR12 and NR22 (N=649)	
Patients with	Total	Possibly related
- AEs*	393 (61%)	124 (19%)
Headache	165 (25%)	11 (2%)
Hemorrhage	69 (11%)	52 (8%)
Nausea	55 (9%)	6 (1%)
Anxiety	52 (8%)	1 (0.2%)
Injection site hemorrhage	43 (7%)	28 (4%)
Dyspepsia	37 (6%)	2 (0.3%)
Bradycardia	36 (6%)	3 (1%)
Hypotension	34 (5%)	1 (0.2%)
- SAEs**	30 (5%)	6 (1%)
- fatal SAEs	5 (1%)	0 (0%)
- discontinuations due to AEs	21 (3%)	15 (2%)

* including SAEs
** including fatal SAEs

Major bleeding occurred in 9 patients (1.4%), and minor bleedings in 110 patients (16.9%) (Tables 4.3 and 4.4, p. 7). Allergic reactions occurred in 2 patients (0.3%). Possible allergic reactions occurred in 34 patients (5.2%). In 4 of these cases (0.6%), the events were possibly related to lepirudin (Tables 4.5a, 4.5b, 4.6a and 4.6b, p.8,9).

1.4.6. Safety experience during or after treatment with lepirudin in other indications

Therapy and prophylaxis of DVT: No further studies have been performed since September 1966, therefore the ISS remains unchanged.

Hemodialysis: One study (NR6) to establish the minimum effective dose of lepirudin to prevent coagulation in the dialysis circuit included 20 patients who received a single i.v. bolus injection of 0.02 to 0.08 mg/kg. There were no serious adverse events and no bleeding events in this study.

Disseminated Intravascular Coagulation (DIC): One study of 6 patients with DIC was performed in Japan. These patients received a continuous iv infusion of lepirudin at doses of . An ongoing phase II study (NR20) has enrolled 10 patients with DIC who received a continuous iv infusion of lepirudin at doses of AEs were observed in 4 of the 6 patients enrolled. Four patients suffered from bleeding at baseline due to the underlying disease.

CPB: One phase II study (NR24) of 22 patients undergoing open-heart surgery with CPB, 11 treated with lepirudin, was completed by July 1997. The data are being processed. Major bleeding occurred in 1 patient (9.1%).

1.5.0. Display of deaths, drop-outs and other serious adverse events (SAE)

In this section, the observed SAEs from all completed and ongoing studies are presented. Only events observed in the lepirudin treated patients are presented.

1.5.1. Deaths, drop-outs and other SAEs during or after treatment with lepirudin in clinical pharmacology studies

No patient died during the course of the studies. Premature discontinuations due to AEs occurred in 3 healthy subjects due prolonged increase in aPTT values and eosinophilia respectively, and in one subject with kidney disease due to bronchitis. No SAEs, no deaths and no discontinuations due to AEs were reported in Japanese studies in healthy subjects.

1.5.2. Deaths, drop-outs and other SAEs during or after treatment with lepirudin in HAT type II studies

In studies B7 and NRI3, 17 patients (8.6%) died, 71 patients (35.9%) experienced at least on SAE, and in 29 patients (14.6%)) the therapy was discontinued due to AEs (Table 4.2a). The most frequent individual SAE possibly related to treatment with lepirudin was hemorrhage (6.6%). The most frequent outcome were sepsis (6 patients), heart failure (4 patients), multi organ failure (4 patients), and pulmonary embolism (3 patients).

In the ongoing study NR2I, 59 of 183 (32.2%) patients suffered at least one SAE. Twenty-three patients (12.6%) died, and in 19 patients (10.4%), study medication was discontinued permanently due to an AE. The most frequent individual SAE possibly related to treatment with lepirudin was spontaneous major bleeding (9.3%). The most frequent AEs with fatal outcome were multi-

organ failure (5 patients), shock (4 patients), sepsis (2 patients), unclassified major bleeding (2 patients), and other (2 patients). Two fatal bleeding AEs were judged to be possibly related to treatment with lepirudin.

1.5.3. Deaths, drop-outs and other SAEs during or after treatment with lepirudin in conjunction with thrombolysis after myocardial infarction

Sixty lepirudin patients (5.5%) of the controlled studies B1-B3 and NR11 died (e.g., cardiogenic shock, heart failure, hemopericardium, ventricular rupture/pericardial tamponade, cerebral hemorrhage, heart arrest, cerebral ischemia, ventricular fibrillation, and unspecified hemorrhage). Twenty-three cases (2.1%) were considered to be possibly related to treatment with lepirudin.

SAEs occurred in 224 patients (20.5%). The most frequent individual SAE possibly related to treatment with lepirudin was injection site hemorrhage (2.3%).

Premature discontinuation of treatment with lepirudin due to AEs occurred in 128 patients (11.7%). The most frequent event was injection site hemorrhage (3.7%). One patient in the uncontrolled study NR1 died due to complications of a retroperitoneal bleeding and renal failure attributed to lepirudin by the investigator. However, the bleeding occurred during non-study high-dose heparin treatment.

SAEs occurred in 8 patients (20.0%). All except the patient with fatal retroperitoneal bleeding and renal failure were cardiac complications. In one patient (2.5%), study treatment was prematurely discontinued due to an AE.

1.5.4. Deaths, drop-outs and other SAEs during or after treatment with lepirudin in patients with acute coronary syndromes not receiving thrombolysis.

Five (0.8%) of 649 lepirudin patients died. None of these cases was considered to be related to treatment with lepirudin. Thirty patients (4.6%) experienced SAEs, which were possibly related to treatment with lepirudin in 6 of them (9.9%). In 21 patients (3.2%), study drug was permanently discontinued due to an AE which in 15 patients (2.3%) was judged to be possibly related to treatment with lepirudin.

The most frequent SAEs were shock (0.8%), MI (0.6%), GI bleeding (0,5%), unspecified hemorrhage (0.5%), cerebral ischemia (0.5%), and CHF (0.3%).

One hundred seventy patients in the ongoing study NR23 died and in 69 patients, study medication was terminated prematurely due to AEs, mostly bleeding.

1.5.5. Deaths, drop-outs and other SAEs during or after treatment with lepirudin for therapy and prophylaxis of DVT

Two of 149 patients (1.3%) treated with lepirudin died. Seven patients (4.7%) experienced SAEs which in 2 patients (1.3%) were possibly related to

treatment with lepirudin. In 6 patients (4.0%), treatment with lepirudin was prematurely discontinued due to AEs which were judged to be possibly related to treatment with lepirudin in 4 patients (2.7%).

SAEs and AEs leading to discontinuation of study medication included PE in two patients. AEs with fatal outcome were hematuria and acute kidney failure.

1.5.6. Deaths, drop-outs and other SAEs in other indications

No SAEs, no deaths and no discontinuations due to any adverse events were reported in patients on hemodialysis.

Two patients of study NR19 (DIC) and three in study NR20 died. None of the deaths were attributed to treatment with lepirudin.

No deaths occurred in study NR24 (CPB); three patients experienced SAEs.

1.6 Conclusions:

In the HAT-II patient population, bleeding represents the most frequent AE. Major bleeding occurred in 18.2% of patients and minor bleeding occurred in 21.4% of patients.

The overall incidence of major bleeding for the entire patient population treated with Refludan in all studies was 5.1%. Aside from HAT-II patients, the highest incidence of major bleeding (5.3%) occurred in patients with AMI receiving concomitant thrombolytic therapy and the lowest incidence (1.4%) in patients with AMI not receiving thrombolytic therapy .

Allergic and anaphylactic reactions, including possible reactions, were reported in 86 patients (1.8%); 46 of these patients (53.6%) also received thrombolytic therapy and/or contrast media.

Compared to ISS submitted with the NDA 20-883, no significant differences in frequency, distribution or type of AEs or SAE were reported in this SU.

2.0. DRUG MONITORING PROGRAM REFLUDAN; Periodic Report

The European Commission approved Refludan on 3-13-1997 for anticoagulation in adult patients suffering from HAT-II with thromboembolic disease mandating parenteral antithrombotic therapy.

The marketing of Refludan was conditioned to a two year committment of drug monitoring program (DMP) with reporting of data at 6, 12 and 24 months. Each participating physician is provided with a study book containing CRF and instructions, and an information brochure containing a "Dear Doctor" letter, an investigational plan and a package insert. The sponsor (HMH) is responsible for the collection of the CRFs. The DMP is currently ongoing in Austria and Germany.

The objective of the DMP was to collect the following parameters for HAT-II patients as mandated by the EMEA:

-Dosage of Refludan used
-Clinical Outcomes: All deaths; limb amputations, new thromboembolic complications (TEC) and major bleeding, and
-to confirm the tolerance and efficacy of Refludan in the routine conditions of medical practice.

The patients entered in the DMP must have the diagnosis of HAT-II confirmed by HIPAA or equivalent test. Refludan is administered at the dose of 0.4 mg/kg iv bolus followed by infusion of 0.15 mg/kg/h for 2 to 10 days.

The CRFs include demographic data, medical history, clinical outcome, and AEs. SAEs must be reported within 24 hours and fully described in the CRFs.

The first 6 month report (5-20-1997 to 9-13-1997) included 101 patients: 40 males and 59 females (mean age 58.6 and 62.2 years); 95% or more Caucasian.

A total of 63 (62.4%) of patients received a bolus dose (mean 0.36 mg/kg), no information was available for 8 patients; 85 patients received the continuous iv infusion, 5 received sc injection, no information for 10. The duration of the infusion ranges between 1 and 58 days, mean 10 ± 8 days.

The APTT was prolonged in all patients (mean lowest and highest 1.74-3.06). Dosage information was available for 96 patients. In 27/96 (28.1%) patients the initial dose of lepirudin was continued till the end of therapy, modified in 69 (71.9%) with increase in 9, decrease in 39, and increase followed by decrease in 21 patients. The number of changes in lepirudin dosage occurred up to 5 times in some patients; the majority of patients had up to 3 changes.

Of the 101 patients treated, 12 (11.9%) died.

Cause of Death of Patients during Refludan Treatment

Cause of Death	Number	% of all patients	% of all deaths
Heart Failure	4	4.0	33.3
Multi organ Failure	3	3.0	25.0
Hemorrhage	2	2.0	16.6
New TEC	1	1.0	8.3
Sepsis	1	1.0	8.3
Respiratory Insufficiency	1	1.0	8.3

Four patients (4%) underwent limb amputation: foot in 1 patient, below the knee in 2 and above the knee in 1 patient. None of these 4 patients died.

One patients had ischemic stroke during therapy. Four patients (4%) experienced new TEC, one of these patients died.

Major bleeding occurred in 10 patients (9.9%), two of these patients died.

A total of 27 SAEs were reported in 20 patients.

Serious Adverse Events

Event	Number
Major Bleeding	10
New TEC	4
Multi-organ Failure	3
Heart Failure	3
Acute Renal Insufficiency	3
Stroke	1
Respiratory Insufficiency	1
Sepsis	1
Pulmonary Embolism	1
Total	27

A total of 81 patients (80.2%) did not experience any SAEs, 16 patients (15.8%) experienced 1 SAE, 3 (3%) experienced 2 SAEs and 1 had 5 SAEs.

In total, 21 AEe occurring in 17 patients were possibly attributed to treatment: 8 major bleeding, 7 minor bleeding, 2 events each of fever and allergic reactions, 1 event each of PE and injection site reaction.

Conclusions: The 6-month data collected under the DMP from a group of patients treated under conventional or routine medical care rather than under study conditions appear to be comparable to those obtained in studies B7 and NR13 for both efficacy and safety. The results are still favorable for the treated group compared to historical control. No new unanticipated SAEs were observed. The DMP will continue for the total 2 year period.

5.0 LABELING

The following revisions are recommended for the Refludin package insert:

In the **DESCRIPTION** section:

- the statement referring to Natural hirudin (last sentence in the first paragraph, should indicate how Refludin differs from Natural hirudin.

In the **CLINICAL TRIALS DATA** section:

- On page 5 of the annotated Package Insert, the word 'both' on line 10 of the second paragraph should be omitted.
- On page 7 of the Annotated Package Insert, the cumulative risk of each of the clinical endpoints (i.e., death, TEC, limb amputation) should be described.

In the **WARNING** section:

- On page 8 of the Annotated Package Insert, the entire section **Hemorrhagic Events** should be **bolded.**
- On page 8 of the Annotated Package Insert, the listing of conditions with increased risk of bleeding listed in the third bullet should include 'other neuraxial procedures'.

In the **PRECAUTIONS** section:

- On page 9 of the Annotated Package Insert, in the **Liver Injury** subsection, the effect of the coagulation defects secondary to liver failure should be included as factors that increase the anticoagulant effect of the drug.
- On page 10 of the Annotated Package Insert, in the **Drug Interaction** subsection, the last statement should include drugs that affect platelet function, in addition to Coumarin derivatives, as concomitant treatment that may increase bleeding.
- On page 11 of the Annotated Package Insert, in the **Animal Pharmacology and Toxicology** subsection, it should be stated that the dosage of lepirudin in mg/m²/day quoted from animal studies as being 1.2 fold the total daily dose in humans was calculated on the basis of a body surface area of 1.45 for a 50 kg subject.
- On page 11 of the Annotated Package Insert, in the **Pregnancy** section, the first statement in the second paragraph should be changed to read: 'Lepirudin (1 mg/kg)by intravenous administration crosses the placental barrier in pregnant rats.

In the **ADVERSE REACTIONS** section:

- On page 12 of the Annotated Package Insert, the entire subsection **Hemorrhagic Events** should be **bolded.**

In the **OVERDOSAGE** section:

- On page 15 of the Annotated Package Insert, the statement 'In case of overdose (eg, suggested by excessively high aPTT values) the risk of bleeding is increased. No specific antidote for REFLUDAN is available' should be **bolded.**

6. CONCLUSIONS AND RECOMMENDATIONS

This review has addressed the sponsor's response (Information Amendment dated 11-21-1997) following the approvable letter date 9-8-1997 for Refludan for anticoagulation in patients with HAT-II and associated thromboembolic disease in order to prevent further TECs.

The clinical issues reviewed include the Safety Update for Refludan in HAT-II and other indications, the safety data from the first periodic report of 101 patients from a two-year post-marketing European Drug Monitoring Program, the sponsor's response to the Agency's requests concerning the post-marketing commitments for the evaluation of Refludan for HAT-II patients with isolated thrombocytopenia and Latent HAT-II, the requirements for pediatric labeling, and the revised Package Insert.

The safety data collected for the SU from the NDA studies, from study NR21 and from the EDMP were comparable to those reported in the ISS of the NDA.

Approval of REFLUDAN for anticoagulation in patients with HAT-II and associated thromboembolic disease in order to prevent further thromboembolic complications is recommended.

The REFLUDAN Package Insert should be revises as recommended.

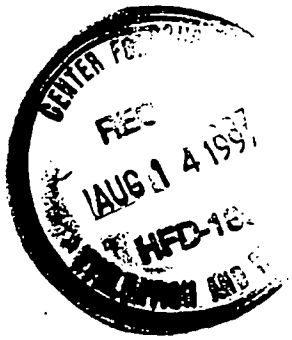
/S/

Lilia Talarico, M.D.

cc:
NDA 20-807
HFD-180
HFD-180/LTalarico
f/t deg: 1/27/98
wpfiles\sulevir.0LT

ClinTrials Research inc.

P.O. BOX 13991 ■ RESEARCH TRIANGLE PARK, NC 27709
ONE COPLEY PARKWAY ■ SUITE 600 ■ MORRISVILLE, NC 27560
PHONE: 919-460-9005 ■ 800-421-1952 ■ FAX: 919-380-1840



August 13, 1997

Lilia Talarico, MD, Acting Director
Division of Gastrointestinal and Coagulation Drug Products
HFD-180, Room 6B-24
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-807 Refludan (lepirudin) Sterile Powder
Information Amendment: Request for Categorical Exclusion from Environmental Assessment and Withdrawal of Pending Environmental Assessment

Dear Dr. Talarico:

Reference is made to New Drug Application (NDA) 20-807 submitted by ClinTrials Research, Inc. on December 31, 1996 on behalf of Behringwerke AG, Marburg, Germany. ClinTrials Research, Inc. is the U.S. agent for Behringwerke AG.

Pursuant to 21 CFR 25.15(d) as published in Federal Register Notice 40570, July 29, 1997, we claim categorical exclusion from the environmental assessment requirement. This compound qualifies for categorical exclusion under subpart C, Section 25.31(b).

We attest that the estimated concentration of lepirudin at the point of entry into the aquatic environment will be below 1 part per billion. Additionally, we are not aware of the existence of any extraordinary circumstances that would preclude this product qualifying for categorical exclusion.

Concurrent with the determination of categorical exclusion we request withdrawal of the environmental assessment submitted with the original application. We waive our claim for exclusion if a FONSI has been signed on or before August 28, 1997.

Other ClinTrials Research locations:

ONE BURTON HILLS BLVD. ■ SUITE 210 ■ NASHVILLE, TN 37215
PHONE: 615-665-9665 ■ 800-346-7931 ■ FAX: 615-665-9676

2365 HARRODSBURG ROAD ■ SUITE A-290 ■ LEXINGTON, KY 40504
PHONE: 606-224-2400 ■ 800-257-5859 ■ FAX: 606-224-2430

KING'S CHASE ■ 2ND FLOOR ■ 107/123 KING STREET
MAIDENHEAD, BERKSHIRE, ENGLAND SL6 1DP
PHONE: (44) 1628 789999 ■ FAX: (44) 1628 789666

ALMA SQUARE ■ LENNEKE MARELAAN 2 A, BOX 1-4
1932 ZAVENTEM, BELGIUM
PHONE: 32 2 7145050 ■ FAX:32 2 7145027

Thank you in advance for your efforts in this regard.

If any questions should arise concerning this submission, please contact Mr. Don Grilley at 919-462-2342 or Mr. Randall Vestal at 919-462-2429.

Sincerely,

Donald G Grilley

APPEARS THIS WAY
ON ORIGINAL

Donald G. Grilley, R.Ph., M.A.
Senior Consultant, Strategic Regulatory Affairs
ClinTrials Research, Inc.

APPEARS THIS WAY
ON ORIGINAL

C20
DuBeau

NDA 20-807

Hoechst Marion Roussel
C/O ClinTrials Research, Inc. (U.S. Agent)
Attention: B. Randall Vestal
P.O. Box 13991
Research Triangle Park, North Carolina 27709

FEB 11 1998

Dear Mr. Vestal:

Please refer to your pending December 31, 1996, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Refludan®
[lepirudin (rDNA) for Injection].

We also refer to your November 21, 1997, submission which includes revised draft labeling in response to the September 8, 1997, approvable letter. We have completed our review of the labeling in this submission and request that you submit revised labeling for the following sections of the proposed package insert:

1. In the CLINICAL TRIAL DATA section, provide information on the incidence of each of the clinical endpoints (i.e. death, TEC, limb amputation).

2. In the PRECAUTIONS section, in the "Liver Injury" subsection, clarify how liver injury decreases renal excretion. In addition, include the effect of the coagulation defects secondary to liver failure as factors that increase the anticoagulant effect of the drug.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact Julieann DuBeau, Regulatory Health Project Manager, at (301) 443-0487.

Sincerely yours,

/S/ 2-11-98

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc:

Original NDA 20-807
HFD-180/Div. Files
HFD-180/CSO/J.DuBeau /S/ 2/11/98
HFD-180/Talarico
r/d Init: Talarico 2/11/98
JD/February 11, 1998 (drafted)
JD/2/11/98/c:\wpfiles\nda\20807802.0jd

GENERAL CORRESPONDENCE

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

NDA 20-807

NOV 28 1997

NOV 28 1997

Hoechst Marion Roussel
C/O ClinTrials Research, Inc. (U.S. Agent)
Attention: B. Randall Vestal
P.O. Box 13991
Research Triangle Park, North Carolina 27709

Dear Mr. Vestal:

We acknowledge receipt on November 24, 1997, of your November 21, 1997, amendment to your new drug application (NDA) for Refludan® [lepirudin (rDNA) for Injection].

This amendment, in combination with your amendment dated October 2, 1997, constitutes a full response to our September 8, 1997, approvable letter. Therefore, the due date under the Prescription Drug User Fee Act of 1992 (PDUFA) is May 24, 1998.

If you have any questions, please contact me at (301) 443-0487.

Sincerely yours,

APPEARS THIS WAY
ON ORIGINAL

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:
Original NDA 20-807
HFD-180/Div. Files
HFD-180/CSO/J.DuBeau
HFD-180/Talarico
DISTRICT OFFICE
JD/November 26, 1997 (drafted)
JD/11/28/97/c:\wpfiles\nda\20807711.0jd

/S/ 11/28/97

APPEARS THIS WAY
ON ORIGINAL

ACKNOWLEDGEMENT (AC)

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: August 25, 1997 AUG 26 1997

FROM: Pharmacology Team Leader
Division of Gastrointestinal and
Coagulation Drug Products, HFD-180

SUBJECT: NDA 20,807 (Refludan) - Comments of Dr. DeGeorge on Draft Labeling

TO: NDA 20,807

The following addresses Dr. DeGeorge's comments and suggestions regarding the labeling and the pharmacology review by Dr. T. Ahmad of the above application.

Suggestion 1

Labeling Page 12, "Subsection 7.7 Animal Data": The present draft labeling in the action package is reproduced below.

7.7 Animal Data

Local Tolerance

Generally, the i.v. route was well tolerated, but in rats and rabbits i.v. administration of Refludan® frequently produced hemorrhage at the injection site. Local edema and sinus histiocytosis in the regional lymph node occurred in some animals.

In Cynomolgus monkeys hematomas and indurations at the injection site were reported after i.v. use.

General Toxicity

Single and repeat-dose toxicity studies in mice, rats and monkeys showed the adverse responses that could be expected from an exaggerated pharmacodynamic impact of Refludan®. In monkeys retinal hemorrhages occurred. Moreover, in rats slight to moderate sinushistiocytosis of the regional lymph nodes and decreased hemosiderin deposits in the spleen were observed. Antibodies against hirudin which appeared in several of the treated monkeys resulted in prolongation of the terminal half-life and an increase in systemic exposure to lepirudin.

Dr. DeGeorge suggests that the title of this subsection should be changed from "Animal data" to "Animal pharmacology and toxicology" and relocated to the end of labeling following the "How supplied" information. The title "Animal pharmacology and toxicology" would be more appropriate than the title "Animal data". CFR, Part 201.57 gives the option of including such information in one or more of the other sections of the labeling as appropriate. In this case the appropriate location appears to be under "PRECAUTIONS" section to follow "7.3 Drug Interactions" subsection and precede the subsection "Carcinogenesis, Mutagenesis, Impairment of Fertility". There is also reference to this subsection of "Animal Data: General Toxicity" in "7.1 General Subsection". The title of the referred subsection needs to be changed. It is therefore recommended that the subsection "Animal Pharmacology and Toxicology" be moved to a location to follow subsection "7.3 Drug Interaction" and precede subsection "Carcinogenesis, Mutagenesis and Impairment of Fertility".

7.4 Animal Pharmacology and Toxicology

Local Tolerance

Generally, the i.v. route was well tolerated, but in rats and rabbits i.v. administration of Refludan® frequently produced hemorrhage at the injection site. Local edema and sinus histiocytosis in the regional lymph node occurred in some animals.

In Cynomolgus monkeys hematomas and indurations at the injection site were reported after i.v. use.

APPEARS THIS WAY ON ORIGINAL

APPEARS THIS WAY ON ORIGINAL

General Toxicity

Single and repeat-dose toxicity studies in mice, rats and monkeys showed the adverse responses that could be expected from an exaggerated pharmacodynamic impact of Refludan®. In monkeys retinal hemorrhages occurred. Moreover, in rats slight to moderate sinushistiocytosis of the regional lymph nodes and decreased hemosiderin deposits in the spleen were observed. Antibodies against hirudin which appeared in several of the treated monkeys resulted in prolongation of the terminal half-life and an increase in systemic exposure to lepirudin.

Suggestions 2 and 3

Dr. DeGeorge suggests that maternal deaths at delivery and parturition should be described either in the Pregnancy section under the title "nonteratogenic effects" or "labor and delivery" and the Pharmacology Team Leader should write an addendum on the findings during parturition.

These comments relate to "Study 12506RSR" (NDA Volumes 1.57 and 1.58) in which pregnant rats were treated from day 6 of gestation through lactation, i.e. for a period of about 17 days during pregnancy and 21 days during lactation. There were 25 animals (#L28494 to L28518) in the high dose group (30 mg/kg/day) at the start of treatment. The average length of gestation was 21 - 22 days in this group which was comparable to that in control group animals. Among the 25 animals of the 30 mg/kg/day group, 7 animals died during pregnancy, 1 animal died on day 1 post-partum and another animal died on day 5 post-partum. Among the 7 deaths during pregnancy, only 2 were ascribed to dystocia. Although the 9 deaths of this group during pregnancy and post-partum periods were identified as treatment related in most of the animals, no ante-mortem clinical signs or macroscopic findings at necropsy were noted and the factors contributing to death could not be determined. The pharmacology reviewer acknowledged these deaths as maternal toxicity related but appropriately removed those findings from "Pregnancy. Teratogenic effects. Pregnancy category" subsection since the findings have no relevance to teratogenic potential of the drug.

As per 21 CFR, Part 201.57 the findings need to be included under "Labor and delivery" only if the drug has a recognized use during labor or delivery (vaginal or abdominal delivery). Since it is unlikely that lepirudin will be used during labor or delivery because of its anticoagulant effect, description of the treatment related mortalities under this heading is not appropriate. It would, however, be appropriate to indicate the findings of deaths of dams under "Nonteratogenic effects" with a clear indication that the deaths were due to undetermined causes.

Recommended Addition to Pregnancy Section (Pages 11 and 12)

"Nonteratogenic effects: In pregnant rats, i.v. administration of lepirudin at 30 mg/kg/day (180 mg/m^2/day 1.2 times the recommended maximum human total daily dose based on body surface area) during organogenesis and perinatal-postnatal periods increased mortality due to undetermined causes."

/S/ -8/26/97

Jasti B. Choudary, B.V.Sc., Ph.D.

APPEARS THIS WAY
ON ORIGINAL

cc:
NDA
HFD-180
HFD-181/CSO
HFD-180/Dr. Choudary
HFD-180/Dr. Talarico
HFD-103/Ms. Collier

APPEARS THIS WAY
ON ORIGINAL

JBC/hw/8/26/97
C:\WPFILES\PHARM\N\20807708.0JC

MEMORANDUM OF TELECON

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

DATE: March 6, 1998

TO: Don Grilley, Regulatory Affairs, Hoechst Marion Roussell

FSI 3/6/98

FROM: Bronwyn Collier, Associate Director for Regulatory Affairs, Office of Drug Evaluation III

SUBJECT: Established name for Refludan

APPEARS THIS WAY
ON ORIGINAL

TO: NDA 20-807

Background: Concerns were raised by the applicant in a facsimile transmission received March 5, 1997, regarding inclusion of "rDNA" in the established name for Refludan. The chemist's review dated March 5, 1998, indicated that rDNA should be retained in the established name. I consulted with Drs. Eric Sheinin, Director, and Yuan Yuan Chiu, Deputy Director, of the Office of New Drug Chemistry, regarding the firm's concerns. It was agreed that "rDNA should be retained in the established name to differentiate the product from other products not manufactured by recombinant technology. In addition, I consulted with Mr. Dan Boring, Chair, Nomenclature Committee, and Mr. Steve Sherman, a reviewer in the Division of Drug Marketing, Advertising, and Communication. They confirmed that the established name, "lepiruden (rDNA) for injection" includes the information contained in the parentheses and should be displayed in its entirety.

Call: I informed Mr. Grilley that the established name for Refludan would continue to include the term "rDNA" as this was a class issue and ample precedent had been established for this terminology. However, alternative wording for the established name, [lepiruden for injection (rDNA origin)] instead of (lepiruden (rDNA) for injection), would be acceptable. Mr. Grilley indicated that either version would be accepted.

I also informed Mr. Grilley that the applicant has the option of submitting a supplement after application approval with information supporting a change in the established name for our review, or, a citizen's petition regarding inclusion of "rDNA" in the established names for products manufactured by recombinant technology.

APPEARS THIS WAY
ON ORIGINAL

CC:
Archival NDA 20-807
HFD-180/Division Files
HFD-180/PM/Julie Dubeau
M.Ysern
HFD-103/subject file
P.Botstein
BC/3/6/98

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

NDA 20-807

Food and Drug Administration
Rockville MD 20857

Hoechst Marion Roussel
C/O ClinTrials Research, Inc. (U.S. Agent)
Attention: B. Randall Vestal
P.O: Box 13991
Research Triangle Park, North Carolina 27709

AUG 19 1997

Dear Mr. Vestal:

We acknowledge receipt on August 15, 1997, of your August 14, 1997, correspondence notifying the Food and Drug Administration of the change of ownership of the following new drug application (NDA):

Name of Drug: Refludan® (lepirudin) Injection

NDA Number: 20-807

Date of Submission: December 31, 1996

Date of Receipt: December 31, 1996

APPEARS THIS WAY
ON ORIGINAL

Name of New Owner: Hoechst Marion Roussel

Name of Previous Owner: Behringwerke AG

Your correspondence provided the information necessary to effect this change and we have revised our records to indicate Hoechst Marion Roussel as the sponsor of record for this application, effective August 15, 1997.

If you have any questions, please contact me at (301) 443-0487.

APPEARS THIS WAY
ON ORIGINAL

Sincerely yours,

APPEARS THIS WAY
ON ORIGINAL

/S/

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

NDA 20-807

Behringwerke AG
C/O ClinTrials Research, Inc. (U.S. Agent)
Attention: B. Randall Vestal
P.O. Box 13991
Research Triangle Park, North Carolina 27709

AUG 11 1997

Dear Mr. Vestal:

Please refer to your pending December 31, 1996, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Refludan® (lepirudin) Injection.

We also refer to your amendments dated February 21, April 24, and April 30, 1997.

We have completed our review of the chemistry, manufacturing, and controls (CMC) and microbiology sections of your submission. The following items must be adequately addressed as soon as possible:

APPEARS THIS WAY
ON ORIGINAL

A. DRUG SUBSTANCE:

1. Clarify whether working reference standards will be used which are assayed , and if so, provide the protocol and results for their validation.

2. Clarify what is used as the drug substance container. Section 3.A.3.d. (vol. 1.5, p.108) specifications for a

3. Clarify which container, , was used for the stability of the

B. DRUG PRODUCT:

Provide complete information relating to system suitability for the following analytical methods: Q-11-070 and Q-11-078

C. MICROBIOLOGY:

1. Submit validation data

Indicate the number and location of

the Specify the
of the biological indicators used.

2. Provide validation data supporting holding time (one week) at 2-8°C in room 110 before filling.

The following items should be addressed at your earliest opportunity:

1. Provide a list of all samples that will be needed for validation of each of the analytical methods. The list should include lot number, identity, size, and quantity for the drug substance, drug product, and reference standards and blanks as stated under 21 CFR 314.50(e).

2. Provide updated methods validation volumes including both the detailed protocol (so it can be reproduced by the FDA Laboratories), followed by the validation report for each method.

Please note that the stability data submitted in the application is sufficient to support an expiry period of 24 months for the 2 ml glass vial with a rubber stopper and aluminum crimp cap.

We would appreciate your prompt written response.

If you have any questions, please contact Julieann DuBeau, Regulatory Health Project Manager, at (301) 443-0487.

Sincerely yours,

/S/

8/11/97

APPEARS THIS WAY
ON ORIGINAL

Eric P. Duffy, Ph.D.
Chemistry Team Leader
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-807
HFD-180/Div. Files
HFD-180/CSO/J.DuBeau
HFD-180/Duffy
HFD-180/Ysern
HFD-520/S.Moore

APPEARS THIS WAY
ON ORIGINAL

HFD-820/ONDC Division Director (only for CMC related issues)
HFD-160/P.Hughes /S/ 8/11/97
r/d Init: Duffy 8/11/97
JD/August 11, 1997 (drafted)
JD/8/11/97/c:\wpfiles\nda\20807708.0jd

INFORMATION REQUEST (IR)

NDA 20-807

MAY 20 1997

ClinTrials Research Inc.
Attention: B. Randall Vestal
Sr. Director, Strategic Regulatory Affairs
P.O. Box 13991
Research Triangle Park, NC 27709

Dear Mr. Vestal:

We acknowledge receipt on May 15, 1997 of your May 13, 1997 amendment to your new drug application for Refludan® (lepirudin) Sterile Powder for Injection or Infusion.

This amendment includes the final study report of the second study in patients with HAT type II (HBW023/7MN-301WC; labeled in the NDA as study NR13) and a meta-analysis of the results of the first (B7) and second (NR13) studies in patients with HAT type II. We consider this a major amendment received by the agency within three months of the user fee due date. Therefore, the user fee clock is extended three months. The new due date is September 30, 1997.

If you have any questions, please contact Michael Folkendt, Project Manager, at (301) 443-0487.

Sincerely yours,

/S/ 5-16-97

Lilia Talarico, M.D.
Acting Director
Division of Gastrointestinal and
Coagulation Drug Products, HFD-180
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

cc:
Original NDA 20-807
HFD-180/Div. Files
HFD-180/M.Folkendt
DISTRICT OFFICE

/S/ 5/16/97

APPEARS THIS WAY
ON ORIGINAL

Drafted by: MF/May 16, 1997/20807705.2mf
Initialed by: L.Talraico 5/16/97
final: 5/16/97

REVIEW EXTENSION

Folkendt

NDA 20-807

MAR - 7 1997

ClinTrials Research Inc.
Attention: B. Randall Vestal
Sr. Director, Strategic Regulatory Affairs
P.O. Box 13991
Research Triangle Park, NC 27709

Dear Mr. Vestal:

Please refer to your pending December 31, 1996 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Refludan® (lepirudin) Sterile Powder for Injection or Infusion.

We also refer to your correspondence dated February 17, 1997 proposing to provide safety update data for the 4-month safety update from only the two clinical studies of the claimed indication, heparin-associated thrombocytopenia (HAT) type II.

Because this application is being reviewed as a priority application with a 6-month user fee goal date, we waive the requirement for you to submit the 4-month safety update report and request that a full safety update, as required under 314.50(d)(5)(vi), be submitted following receipt of an approvable letter.

If you have any questions, please contact Michael Folkendt, Project Manager, at (301) 443-0487.

Sincerely yours,

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Stephen B. Fredd, M.D.
Director
Division of Gastrointestinal and Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Original NDA 20-807
HFD-180/Div. Files
HFD-180/CSO/M.Folkendt
HFD-180/L.Talarico

/S/ 3/6/97

APPEARS THIS WAY
ON ORIGINAL

Drafted by: mf/February 26, 1997/20807702.amf
Initialed by: L.Talarico 2/27/97
S.Fredd 3/5/97
final: 3/6/97

/S/ 3/6/97

GENERAL CORRESPONDENCE (GC)

DuBeau

NDA 20-807

Behringwerke AG
C/O ClinTrials Research, Inc. (U.S. Agent)
Attention: B. Randall Vestal
P.O. Box 13991
Research Triangle Park, North Carolina 27709

JAN - 7 1997

Dear Mr. Vestal:

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: Refludan® (lepirudin) Injection

Therapeutic Classification: Priority

Date of Application: December 31, 1996

APPEARS THIS WAY

Date of Receipt: December 31, 1996

Our Reference Number: 20-807

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 March 1, 1997, in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102© 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. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact me at (301) 443-0487.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

APPEARS THIS WAY

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:
Original NDA 20-807
HFD-180/Div. Files
HFD-180/CSO/J.DuBea 1/7/97
DISTRICT OFFICE
JD/January 7, 1997 (drafted)
JD/1/7/97/c:\wpfiles\nda\20807701.0jd

ACKNOWLEDGEMENT (AC)

APPEARS THIS WAY
ON ORIGINAL

Folkendt 758

REQUEST FOR TRADEMARK REVIEW

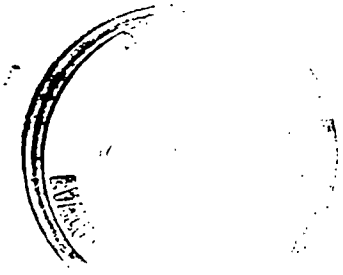
To: Labeling and Nomenclature Committee
Attention: Dan Boring, Chair (HFD-530), 9201 Corporate Blvd, Room N461

From: Division of Gastrointestinal and Coagulation Drug Products	**HFD-180**
Attention: Michael Folkendt, Project Manager	**Phone:** (301) 443-0487
Date: February 5, 1997 MF 2/5/97	
Subject: Request for Assessment of a Trademark for a Proposed New Drug Product	
Proposed Trademark: Refludan®	**NDA/ANDA#** 20-807
Established name, including dosage form: Lepirudin Sterile Powder for Injection or Infusion	
Other trademarks by the same firm for companion products: -none-	
Indications for Use (may be a summary if proposed statement is lengthy): Treatment (anticoagulation) of heparin-associated thrombocytopenia (HAT) type II and thromboembolic disease in adult patients. This is a priority application (with a potential orphan designation).	
Initial Comments from the submitter (concerns, observations, etc.): This product is a recombinant Hirudin product. For your information, I have attached a copy of the cover letter, draft labeling, pharmacological class, & part of the CMC summary describing the drug substance submitted in this application.	

Note: Meetings of the Committee are scheduled for the 4th Tuesday of the month. Please submit this form at least one week ahead of the meeting. Responses will be as timely as possible.

cc: Original 20-807; HFD-180/division file; HFD-180/M.Folkendt; HFD-180/M.Ysern, HFD-510/S.Moore

Rev. December 95



Consult #758 (HFD-180)

REFLUDAN lepirudin sterile powder for injection

The following look-alike/sound-alike conflicts were noted: RELAFEN, RIFADIN, RIFAMPIN, DIFLUCAN, and FLUDARA. However, the Committee feels there is a low potential for confusion between these names. There were no misleading aspects found in the proposed proprietary name.

The word "sterile" is no longer used by USP in monograph titles. The appropriate established name for this product should be "lepirudin for injection" to be in conformance with USP parenteral nomenclature.

The Committee has no reason to find the proposed proprietary name unacceptable.

D U Boring 3/27/97, Chair
CDER Labeling and Nomenclature Committee