

121

7/17/98

Julieann DuBeau, RN, MSN
Regulatory Health Project Manager

Attachment: September 14, 1998, facsimile

cc: Original NDA 20-883
HFD-180/Div. File
HFD-180/DuBeau
HFD-180/Talarico
HFD-180/Gallo-Torres
HFD-180/Robie-Suh
JD/September 17, 1998 (drafted)
JD/9/17/98/

TELECON

Handwritten mark

MEMORANDUM OF TELECON

DATE: May 8, 1998

APPLICATION NUMBER: NDA 20-883; Novastan® (argatroban) Injection

BETWEEN:

Name: Mr. G. Knappenberger; Senior Director, Clinical Development & Regulatory Affairs

Dr. R. Schwarz; Vice President, Clinical Development & Regulatory Affairs

Phone: (713) 796-8822

Representing: Texas Biotechnology Corporation

AND

Name: Ms. J. DuBeau; Regulatory Health Project Manager

Dr. L. Talarico; Division Director

Dr. E. Duffy; Chemistry Team Leader

Ms. B. Collier; Associate Director for Regulatory Affairs, ODE III

Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Issuance of an action letter for NDA 20-883

BACKGROUND:

On August 11, 1997, Texas Biotechnology Corporation submitted an NDA for Novastan® Injection with the following proposed indication: Anticoagulant therapy in patients with heparin-induced thrombocytopenia. The PDUFA due date is May 15, 1998.

TODAY'S PHONE CALL:

Dr. Talarico stated that the information submitted under NDA 20-883 has been reviewed and does not support the proposed indication. Thus, the firm will be receiving a NOT APPROVABLE action letter today. She encouraged the firm to request a formal meeting to discuss strategies for resolution of issues which may ultimately lead to the demonstration of safety and efficacy of Novastan® Injection in patients with heparin-induced thrombocytopenia. Mr. Knappenberger stated that he will request a formal meeting on behalf of the firm.

 /S/ 5/27/98
Julfeann DuBeau, RN, MSN
Regulatory Health Project Manager

cc: Original NDA 20-883

HFD-180/Div. File

HFD-180/DuBeau

HFD-180/Talarico

r/d Init: Talarico 5/26/98

JD/May 22, 1998 (drafted)

JD/5/27/98/ ~~_____~~

TELECON

D. J. Sizer

MEMORANDUM OF TELECON

DATE: March 26, 1998

APPLICATION NUMBER: NDA 20-883; Novastan® (argatroban) Injection

BETWEEN:

- Name: Mr. G. Knappenberger; Senior Director, Clinical Development & Regulatory Affairs, TBC
- Dr. R. Schwarz; Vice President, Clinical Development & Regulatory Affairs, TBC
- Dr. J. Becker; Senior Director, Clinical Research, TBC
- Ms. K. Clark; Director of North American Regulatory Affairs, SKB
- Dr. S. Sheth; Associate Director, Clinical Pharmacology, SKB
- Dr. B. Ison; Director, Cardiovascular Therapeutic Unit, SKB
- Dr. W. Matthews; Director, New Product Management, SKB
- Ms. N. Blackman; Senior Biostatistician, Biometrics & Statistical Scientist, SKB

Phone: (713) 796-8822

Representing: Texas Biotechnology Corporation (TBC) & SmithKline Beecham Pharmaceuticals (SKB)

AND

- Name: Ms. J. DuBeau; Regulatory Health Project Manager
- Dr. L. Talarico; Division Director
- Dr. K. Sizer; Medical Officer
- Dr. A. Sankoh; Statistical Team Leader

Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Status of pending NDA

BACKGROUND:

On August 11, 1997, TBC submitted an NDA for Novastan® Injection with the following proposed indication: Anticoagulant therapy in patients with heparin-induced thrombocytopenia. The firm's NDA is based on the single, historically controlled, pivotal study, ARG-911, entitled "An Open-label Study of NOVASTAN® (brand of argatroban) in Patients with Heparin-induced Thrombocytopenia (HIT) or Heparin-induced Thrombocytopenia and Thrombosis Syndrome (HITTS)." On December 23, 1997, the

PDUFA review clock was extended by three months due to the submission of safety and efficacy information for 174 patients enrolled in Study ARG-915, entitled "An Open-Label Clinical Study of NOVASTAN® in Patients with Heparin-Induced Thrombocytopenia (HIT)/Heparin-Induced Thrombocytopenia and Thrombosis Syndrome (HITTS)." Study ARG-915 is the open-label continuation of the pivotal study ARG-911. The new PDUFA due date is May 15, 1998. SKB is TBC's corporate development and marketing partner. Mr. Knappenberger called and requested further information regarding the status of the pending NDA.

TODAY'S PHONE CALL:

Dr. Talarico stated that the division is concerned with the incidence of deaths in both ARG-911 and ARG-915 studies. In the ARG-911 study, the incidence of deaths was higher than expected in the argatroban treated group as compared to the historical control group. Even though patients in the argatroban treated group were sicker, concomitant factors do not appear to have contributed to these deaths. The division had requested data from the ARG-915 study hoping to alleviate the concerns regarding the incidence of deaths, however, deaths were again higher in the argatroban treated group as compared to the historical control group even though patients in the historical control group were sicker. Dr. Talarico acknowledged that study ARG-915 was not intended to demonstrate efficacy, only safety. In addition, she stated that some of the NDA reviews are not finalized and the action package still needs to be reviewed at the office level.

The firm stated that the covariate analysis should have explained the difference in all cause mortality between the two groups at baseline. In study ARG-911, Dr. Sankoh stated that the covariate analysis results were inconsistent, and failed to provide an adequate explanation for the difference in the HIT population. The results were a little more comforting for the HITTS population. In study ARG-915, Dr. Sizer stated that the covariate analysis did not support the efficacy of argatroban in either the HIT or HITTS population. Dr. Sankoh clarified that the additional efficacy and safety information provided in study ARG-915 failed to clarify the issues raised in study ARG-911. Thus, the two studies do not appear to provide adequate safety and efficacy support even in the HITTS population. Dr. Sizer stated that of the 271 patients enrolled in the ARG-915 study, data for the first 174 patients have been submitted for review. A mortality rate of 27% has been reported for the remaining 97 patients to date. The firm stated that they could submit the safety information on these additional cases for review. Dr. Sizer stated that although the division is very interested in reviewing the additional 97 cases for study ARG-915, no further information can be reviewed during this review cycle. Dr. Talarico stated that the firm should wait for the action letter, and then provide this additional information. In addition, the firm may obtain a copy of all reviews upon issuance of the first action letter.

/S/

3/31/98

Julieann DuBeau, RN, MSN

Regulatory Health Project Manager

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/S/

3-31-98

cc: Original NDA 20-883

HFD-180/Div. File

HFD-180/DuBeau

HFD-180/Sizer

r/d Init: Talarico 3/30/98

r/d Init: Sizer 3/30/98

r/d Init: Sankoh 3/30/98

JD/March 27, 1998 (drafted)

JD/3/31/98/

IS/ 3-31-98

TELECON

DuBeau

MEMORANDUM OF TELECON

DATE: July 18, 1997

APPLICATION NUMBER: _____ NOVASTAN® (argatroban) Injection

BETWEEN:

Names: Mr. G. Knappenberger; Senior Director, Clinical Development & Regulatory Affairs, TBC
Dr. R. Schwarz; Vice President, Clinical Development & Regulatory Affairs, TBC
Ms. C. Clark; Director, North American Regulatory Affairs, SKB
Dr. D. Garver; Project Director, Research & Development, SKB
Dr. J. Granett; Group Director, Cardiopulmonary Therapeutic Unit, Clinical Research, Development, and Medical Affairs, SKB

Phone: (713) 796-8822

Representing: Texas Biotechnology Corporation (TBC) & SmithKline Beecham Pharmaceuticals (SKB).

AND

Names: Ms. J. DuBeau; Regulatory Health Project Manager
Dr. L. Talarico; Acting Division Director
Dr. K. Sizer; Medical Officer
Dr. N. Markovic; Medical Officer
Dr. A. Sankoh; Statistical Reviewer

Representing: Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Clarification of Issues Discussed at the May 21, 1997, Pre-NDA Meeting.

BACKGROUND:

This IND was submitted December 8, 1988, by _____ and subsequently transferred to TBC on July 26, 1993. SKB is TBC's potential corporate development and marketing partner. The compound is a synthetic thrombin inhibitor derived from L-arginine. According to the firm, at therapeutic doses, it inhibits all physiologic effects of thrombin, including conversion of fibrinogen to fibrin, platelet aggregation, and activation of Factors XIII and VIII. NOVASTAN® is under development as a therapeutic agent for the treatment of thromboembolism associated with heparin-induced thrombocytopenia and thrombosis syndrome (HITTS) as well as prophylaxis of thromboembolism in patients with heparin-induced

thrombocytopenia (HIT). For the purpose of this memorandum, in the clinical setting, both HIT and HITTS are referred to globally as HIT. The proposed indication is "anticoagulant therapy in patients with HIT" which is based upon the single, historically controlled, pivotal study ARG-911 entitled, "An Open-Label Study of NOVASTAN in Patients with HIT and HITTS." The projected date for NDA submission is August 1997. The firm has requested this teleconference to clarify issues discussed at the May 21, 1997, Pre-NDA meeting.

TODAY'S PHONE CALL:

The firm posed three questions to the Agency as outlined in their July 25, 1997, submission (serial number 136, received via fax on 7/15/97). See attachment.

1. "Can you confirm that the Division will accept for filing our NDA based on the results of the ARG-911 trial which we discussed on May 21, 1997?"

Dr. Talarico stated that an application cannot be refused for filing based upon submission of a single pivotal study. She referred the firm to the Guidance document entitled Draft Guidance: Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products which addresses the issue of one versus two pivotal Phase III studies. She reminded the firm that the application must be complete upon submission, and that comment on the fileability of the application will be reserved until the contents are reviewed.

2. "Does the Division (or the Agency) have any specific criteria and standards for the collection of historical control cases, dealing with issues such as number of centers, number of cases per center, etc.?"

Dr. Talarico stated that there are no official criteria or standards for the collection of historical control cases. The firm agreed that there is an imbalance between the historically controlled population and the NOVASTAN®-treated population, with the latter being more medically compromised at baseline (e.g. incidences of underlying disease and pre-existing conditions). Dr. Talarico suggested that the firm determine if there were any "missed" cases (i.e. not correctly diagnosed with HIT) in the historical control group, and if there were potential candidates who did not receive treatment. She requested information on patient events from the time of "HIT" diagnosis to treatment. The firm stated that there were very few "missed" patients in the historical control group upon re-examination of the information. In addition, according to the firm, the mortality rate in the NOVASTAN®-treated population was comparable to other literature based historical control studies (e.g. lepirudin). In response to a question from Dr. Sizer, the firm stated that when gathering historical control information, the screening criteria included low platelet count and matching administration of heparin. The firm stated that there is no further historical control data to obtain, however, an open-label extension study is in process and has enrolled approximately 150 patients to date. Dr. Talarico requested that the firm submit the results of this extension study as soon as they are available.

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DuBeau

MEMORANDUM OF TELECON

DATE: November 12, 1996

APPLICATION NUMBER: ~~_____~~ Novastan® (argatroban) Injection

BETWEEN:

Name: Mr. Gary Knappenberger, Director, Regulatory Affairs
Phone: (713) 796-8822
Representing: Texas Biotechnology Corporation

AND

Name: Ms. Julieann DuBeau, CSO
Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: One versus Two Pivotal Clinical Trials

BACKGROUND:

On April 2, 1996, an End-of-Phase II meeting was held with Texas Biotechnology Corporation to discuss Novastan® Injection, a thrombin inhibitor. On October 31, 1996, the firm submitted a Pre-NDA meeting request in which the following sentence was included in the cover letter: "As was discussed on April 2, it was agreed that this single study can be used under Subpart E to support the review and approval of argatroban in this Life Threatening and Severly-debilitating Condition of HITTS."

TODAY'S PHONE CALL:

Mr. Knappenberger was called and requested to refer to the April 30, 1996, Agency letter containing April 2, 1996, meeting minutes. Specifically, Dr. Fredd explained that drugs could be approved on the basis of a single study, provided that there is a mortality or severely debilitating efficacy endpoint with results that are compelling. He stressed that the company would need to make the case for one study. Mr. Knappenberger stated that he did not intend for the firm's October 31, 1996, letter to imply that the Agency agreed that one study is adequate for approval.

/s/

= 11/12/96

Ms. Julieann DuBeau
Consumer Safety Officer

cc: Original ~~_____~~
HFD-180/Div. File
HFD-180/DuBeau
HFD-180/Sizer

Memorandum: Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Date: June 20, 2000

From: Ann T. Farrell MD
Medical Officer, Gastrointestinal and Coagulation Drug Products,
HFD-180

To: NDA 20-883

Through: Dr. Lilia Talarico
Division Director, Gastrointestinal and Coagulation Drug Products,
HFD-180

Subject: Mean Activated Partial Thromboplastin Time (aPTT) levels during ARG-911 study listed on TRADEMARK (argatroban) label

The firm was asked to supply additional information in the revised label regarding the mean and median aPTT levels during argatroban infusion. This information will guide the physician using the drug and following aPTT levels. The firm responded with the following:

Evaluation of aPTT levels in Study I HIT patients revealed a mean baseline of 38 as compared with 64 at first assessment *. Median values were 30 and 59 respectively. In HITTS patients, the mean baseline aPTT value was 34 compared to 70 at first assessment *. Median values were 30 and 64 respectively.

(*first assessment was defined as occurring at least two hours post-infusion start-time).

Reviewer's Comment:

This reviewer recommends the following revised paragraph be placed in the package insert.

In Study I, the mean aPTT level for HIT patients was 38 seconds prior to start of argatroban infusion. At first assessment, during the argatroban infusion, mean aPTT level for HIT patients was 64 seconds. Overall, the mean aPTT level during the argatroban infusion for HIT patients was 62.5 seconds. In Study I, the mean aPTT level for HITTS patients was 34 seconds prior to start of argatroban infusion. At first assessment*, during the argatroban infusion, mean aPTT level for HITTS patients was 70 seconds. Overall, the mean aPTT level during the argatroban infusion for HITTS patients was 64.5 seconds.*

*(*first assessment was defined as occurring at least two hours post-infusion start time.)*

/S/

Ann T. Farrell MD

6-20-00

HFD-180
HFD-180/L Talarico */S/ 6-20-00*
HFD-180/S Aurecchia
HFD-180/A Farrell
HFD-181/J DuBeau
HFD-180/J Choudary
HFD-180/L Zhou

MEMORANDUM

From: Ali Al-Hakim, Ph.D.
Date: 06/02/00
To: NDA 20-883
Subject: Batch size for Argatroban Injection

The NDA applicant responded to our information request regarding providing a range for the weight of commercial Argatroban batches (see chemistry review dated May 22, 2000). The attached document (FAX) received from the firm indicated that the final bulk solution weight will range between _____

The information is satisfactory.

/S/ 06/02/00
Ali Al-Hakim, Ph.D.
Review Chemist, HFD-180

CC:
NDA 20-883
HFD-180
HFD-181/CSO J.DuBeau
HFD-180/L.Talarico
HFD-180/AAl-Hakim
HFD-180/L.Zhou *h. jk 6/2/00*
MSWord/NDA 20-883.1aa

Memorandum

Date: 7 February 2000

From: David E. Morse, Ph.D. /S/ 7 Feb. 2000
Asc. Director (Pharm./Tox.), Office of Drug Evaluation III

To: Florence Houn, M.D.
Director, Office of Drug Evaluation III

Cc: Victor Raczowski, Deputy Director, Office of Drug Evaluation III
Lillia Talarico, M.D., Dir., DGCDP (HFD-180)
Jasti Choudary, Ph.D., TL Pharm./Tox., DGCDP (HFD-180)
Julieann DuBeau, RN, MSN, Project Manager, DGCDP (HFD-180)

Subject: NDA 20-883
NOVASTAN® (argatroban) Injection
Review of Pharm./Tox. Information and Sections of Proposed Product Label

I. Materials Included in Review

1. Pharm./Tox. Reviews of NDA 20-883, dated 23 March 1998, written by Indra Antonipillai, Ph.D.
2. Pharm./Tox. Team Leader Label Review of NDA 20-883, written by Jasti Choudary, B.V.Sc., Ph.D., dated 6 January 2000.
3. NDA 20-883 Approval Package, with Draft Product Labeling.

II. Comments and Conclusions

1. A review of the action package for NDA 20-883, NOVASTAN® Injection, suggests that the product has been adequately evaluated in multiple repeat-dose non-clinical safety studies up to 6 months duration for approval of the requested indication (short-term intravenous administration for patients with heparin induced thrombocytopenia who require anticoagulation therapy).
2. The non-clinical safety data do not suggest of a risk of alterations to fertility, or congenital malformations or other alterations to fetal growth or viability, for patients administered NOVASTAN® (argatroban) during or preceding pregnancy. However, because animal data are not always predictive of the human response, some residual level of risk can not be excluded based on the available animal data.
3. Carcinogenicity testing with argatroban (NOVASTAN® Injection) is not required based on the limited duration of exposure for the requested product indication, and the lack of mutagenic or clastogenic activity seen in multiple in vitro and in vivo genotoxicity studies conducted with argatroban.
4. Specific comments related to the product label follow:
 - It is recommended that the genotoxicity studies described in the proposed product label under the heading of "Carcinogenesis, Mutagenesis, Impairment of Fertility", be clearly identified as having been conducted "in vitro" or "in vivo" as is appropriate for each study methodology.

- Under the heading of "Pregnancy Category" it is suggested that the last phrase of the first sentence of the section be simplified to read, "and revealed no evidence of harm to the fetus due to argatroban."
- Under the heading "Nursing Mothers":
 - Reference is made in the proposed product label to argatroban being detected in the milk of lactating rats. It is suggested that the original data for the "lactation" study conducted in rats (referenced on page 38 of the Pharmacology review for argatroban) be reassessed to determine the concentration of drug excreted in rat milk. If the study data are of adequate quality, it is suggested that the label include information regarding the relative milk-to-plasma concentration of argatroban (i.e., below, at or above serum drug concentration).
 - A comparison of the acute toxicity data following IV, IP or oral administration of argatroban to the rat suggests that the oral bioavailability of the product is low (based on the dose differential for the induction of acute toxicity or lethality). It is therefor suggested that the sponsor be asked to supply oral bioavailability data for argatroban in the rat. Inclusion of the non-clinical bioavailability data in the product label will provide additional information about potential drug exposure and risk to a nursing infant.
- It is recommended that all interspecies dose comparisons included in the product label be based on pharmacokinetic parameters (i.e., AUC, C_{max} or other relevant parameter) unless there is clear scientific justification for the use of another scaling method, or there is insufficient pharmacokinetic data to allow for interspecies dose comparisons.

Summary

A review of the action package for NDA 20-883, NOVASTAN® (argatroban) Injection, suggests that the product has been adequately evaluated in multiple repeat-dose non-clinical safety studies up to 6 months duration, along with reproductive and genotoxicity studies, for approval of the requested indication. The proposed product label, with possible revision as suggested in the preceding section, accurately reflects the non-clinical safety data for this product.

APPEARS THIS WAY
ON ORIGINAL

Memorandum: Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Date: January 27, 2000

From: Ann T. Farrell MD, Medical Officer
Gastrointestinal and Coagulation Drug Products, HFD-180

To: NDA 20-883

Through: Dr. Lilia Talarico, M.D., Director
Gastrointestinal and Coagulation Drug Products, HFD-180

Subject: Pediatric Drug Development Plan for Novastan (Argatroban)

Although the number of pediatric patients developing heparin-induced thrombocytopenia may be small compared to the adult population, the need exists for an anticoagulant alternative in these patients.

There is a definite need for information regarding the use of argatroban for heparin-induced thrombocytopenia in the pediatric population for the following reasons:

- 1) children can develop heparin-induced thrombocytopenia
- 2) the dosing recommendations for argatroban in children are likely to be different from the adult recommendations
- 3) some pediatric patients who are intolerant of heparin have need for long-term anticoagulation

1) Children can develop Heparin-Induced Thrombocytopenia

Several papers in the literature document this issue clearly.^{1,2,3,4}

- a) Spadone et. al. described heparin-induced thrombocytopenia in the newborn.¹ The article describes 34 infants (preterm and full term) with thrombocytopenia who developed heparin antibodies, aortic thromboses, and died. The majority of these patients had an umbilical artery catheter.
- b) Potter et. al. described the development of heparin-induced thrombocytopenia and thrombosis in a fourteen year old boy who had a central venous catheter in place.²
- c) Murdoch et. al. described a three-month old and a fourteen year old who developed heparin-induced thrombocytopenia. The three month old developed renal vein thrombosis.³

2) Dosing recommendations for argatroban are likely to differ from the adult recommendations.⁵

It is known that heparin requirements are increased in neonates compared with adults because the clearance of heparin is accelerated in the newborn, plasma concentrations of ATIII are less in premature infants, and studies in newborn piglet animal models have demonstrated that low ATIII levels limit the anticoagulant and antithrombotic effectiveness of heparin. Although argatroban differs from heparin because argatroban is a direct thrombin inhibitor not requiring ATIII, pharmacokinetic information for argatroban is not known in children.

3) Children intolerant to heparin can have long term need for anticoagulation.

Examples of children requiring long term anticoagulation include:

- a) children with malignancy who require venous catheter access
- b) children with congenital heart disease in whom Coumadin is not indicated

/S/

Ann T. Farrell, M.D.

1/27/00

cc:

NDA 20-883

HFD-180

HFD-180/LTalarico

HFD-180/SAurecchia

HFD-180/KRobie-Suh

HFD-180/AFarrell

HFD-181/JDuBeau

HFD-180/JChoudary

HFD-180/LZhou

f/t 1/28/00 jgw

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References

1. Spadone, D; Clark F; James E; Laster J; Hoch J; Silver D. Heparin-Induced Thrombocytopenia in the Newborn. Journal of Vascular Surgery 1992 Feb; 15(2):306-312.
2. Potter, C; Gill JC; Scott, JP; McFarland, JG. Heparin-Induced Thrombocytopenia in a Child. Journal of Pediatrics 1992 Jul; 121(1):135-8.
3. Murdoch I; Beattie R, Silver D. Heparin-Induced Thrombocytopenia in Children. Acta Paediatrica 1993; 82: 495-7.
4. Mocan, H; Beattie T; Murphy A. Renal Venous Thrombosis in Infancy: a long term follow-up. Pediatric Nephrology 1991: 5:45-9.
5. Nathan, DG; Orkin, SH; Oski, FA; Nathan and Oski's Hematology of infancy and childhood. 5th edition. 1998. W.B. Saunders. pp.143-150, 1702-1703.

Memorandum: Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Date: January 27, 2000

From: Ann T. Farrell MD, Medical Officer,
Gastrointestinal and Coagulation Drug Products, HFD-180

To: NDA 20-883

Through: Dr. Lilia Talarico, Director, Gastrointestinal and Coagulation Drug
Products, HFD-180

Subject: OPDRA consult for Novastan® (argatroban) - Potential for medication
errors

The Risk Assessment section of the OPDRA consult was reviewed. OPDRA consult and study focused on the risk of possible medication errors. In my opinion, the administration errors are unlikely to occur for the following reasons.

Novastan (argatroban) will be dispensed exclusively by a hospital pharmacy and administered in the hospital. Hospitals are increasingly requiring physicians to type their orders into computers to decrease confusion seen with handwritten orders or prescriptions.

- a) Considerations for errors pertinent to Novantrone (mitoxantrone)
- 1) The Novantrone concentrate is a sterile, dark blue color compared to the Novastan concentrate, which is clear and colorless.
 - 2) The dark blue color for Novantrone persists after it is diluted. The lack of color for Novastan persists after it is diluted.
 - 3) Novantrone is a chemotherapeutic agent given to patients with breast cancer, acute leukemia, lymphoma, or prostate cancer.
 - 4) Novastan is an anticoagulant for use in patients with heparin-induced thrombocytopenia requiring anticoagulation.
 - 5) Novantrone is dosed in mg/m^2 (body surface area) and given as a short intravenous infusion compared to Novastan, which is dosed as a bolus and continuous infusion in $\mu\text{g}/\text{kg}/\text{min}$.
 - 6) Novastan would be adjusted by daily monitoring of aPTT levels.
 - 7) Novantrone is adjusted based on patient's blood work, cardiac function, and date of last chemotherapy.
 - 8) There is a large black box warning at the beginning of the package insert for Novantrone describing the agent is a chemotherapeutic agent compared to none for Novastan.
 - 9) There is a warning in the indications section (capital letters) in the Novantrone package insert that Novantrone is only to be given by physicians experienced in administering chemotherapy.
 - 10) Chemotherapeutic agents are usually stored separately and reconstituted under a separate hood because of the risk of teratogenicity for pharmacy employees.
 - 11) The recommended reconstitution of Novantrone is in at least 50 mL of 0.9 NS or 5% dextrose this compares to Novastan which is reconstituted in 0.9 NS, Lactated Ringer's, 5% dextrose at 1 mg/mL.
 - 12) Chemotherapy administration is performed by oncology certified nurses who perform a crosscheck with other personnel prior to administration.

- b) Considerations for errors pertinent to (Mevacor) lovastatin
- 1) Lovastatin is a green, blue or orange tablet while Novastan is a clear and colorless concentrate, which must be diluted further to make the continuous infusion.
 - 2) Lovastatin is not dosed by body weight whereas Novastan is dosed in $\mu\text{g}/\text{kg}/\text{min}$.
 - 3) Lovastatin is adjusted by primary care or cardiology physicians based on patient's cholesterol levels whereas Novastan would be adjusted by aPTT levels.
 - 4) Lovastatin is a hyperlipidemic agent for use in patients with types IIa and IIb primary hypercholesterolemia.
 - 5) Novastan is an anticoagulant for use in patients with heparin-induced thrombocytopenia requiring anticoagulation.

/S/

Ann T. Farrell, M.D.

1/27/00

cc:

NDA 20-883

HFD-180

HFD-180/LTalarico

HFD-180/SAurecchia

HFD-180/KRobie-Suh

HFD-180/AFarrell

HFD-181/JDuBeau

HFD-180/JChoudary

HFD-180/LZhou

f/t 1/28/00 jgw

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/SA-28-00

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

DATE: 1-12-2000

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

SUBJECT: NDA 20-883: Argatroban for treatment of heparin-induced thrombocytopenia requiring anticoagulation.

TO: Director Office of Drug Evaluation III

Background Comments:

Heparin induced thrombocytopenia (HIT) is a potentially serious complication of heparin therapy that can occur in about 5% of individuals receiving heparin. About one third of these patients develop venous or arterial thrombotic complications and as many as 25-30% die. Heparin-induced thrombocytopenia associated with thrombotic complications is conventionally indicated as HITTS (Heparin-induced thrombocytopenia and thrombosis syndrome).

Heparin induced thrombocytopenia is mediated through an immune mechanism by which heparin, in combination with a protein released from the alpha granules of activated platelets (platelet factor 4 or PF4), elicits the formation of specific antibodies. The immune complex bind to platelets causing platelet activation, release of platelet-derived procoagulant microparticles, and thrombocytopenia. Endothelial cells surface contain glycosaminoglycans which, like heparin, can bind PF4. Consequently, the immune complex Heparin+PF4/antibody can also bind to the endothelial cell surface causing immune-mediated cellular damage, local platelet adhesion and aggregation, activation of the coagulation mechanism and ultimately local thrombosis (HITTS). Thrombosis can involve both the venous or arterial vasculature with development of DVT, MI, CVA or peripheral ischemia. Thromboembolic events (TEE) are fatal in about 30% of patients or require limb amputation in about 20% of patients. It is still unclear why some patients develop only thrombocytopenia and others develop thrombotic complications. Underlying clinical factors may play a role since surgical patients tend to develop primarily venous thromboses.

The clinical diagnosis of HIT/HITTS is primarily based on the findings of reduction in platelet count below $150 \times 10^9/L$ or to less than 50% baseline. Between one third to one half of patients will present with thrombotic events.

The diagnosis of HIT can be confirmed by laboratory tests that detect heparin/PF4 antibodies by either platelet activation tests (functional assay) or by antigen binding tests (ELISA assay). -

Anti-heparin/PF4 antibodies persist for about three months, therefore immediate and anamnestic reactions on re-exposure to heparin can be anticipated

In patients with uncomplicated heparin-induced thrombocytopenia, discontinuation of heparin will terminate the immune platelet reaction and allow resolution of the thrombocytopenia within 5-7 days. However, the risk of thrombotic complications persists despite normalization of platelet counts. A recent retrospective review of patients with uncomplicated HIT indicates that approximately 50% of patients who initially appeared to respond to discontinuation of heparin with resolution of the thrombocytopenia, developed thromboembolic events within 10 to 30 days from the diagnosis of HIT. Furthermore, the mortality rate in this patient population was approximately 20%. These findings indicate that HIT and HITTS do not represent separate conditions, rather they represent manifestations of a continuum of the same immune reaction.

The management of patients with HIT/HITTS can be very difficult when anticoagulant therapy is needed for thromboprophylaxis or for treatment of TEE once heparin must be discontinued or it cannot be instituted.

In 1997, the recombinant hirudin, Refludan, was approved for the treatment of patients with heparin-induced thrombocytopenia presenting with thromboembolic complications requiring anticoagulant therapy. Approval was based on the efficacy and safety results of two prospective studies that showed reduction of composite endpoint of death, amputation or new thromboembolic events, compared to an historical control. Patients eligible for the historical control were selected from a registry of HIT/HITTS patients not treated with Refludan.

Refludan is a direct, irreversible thrombin inhibitor with dose-related anti-thrombin activity. The compound has a half-life of 1.3 hours and is excreted primarily by the kidneys. Refludan does not cross-react with heparin/PF4 antibodies, however it is antigenic and stimulates specific IgG antibodies production in more than 40% of patients. The clinical significance of these antibodies is still unclear, however they may enhance the anticoagulant activity of Refludan. Due to its renal excretion, plasma concentration and anticoagulant effect, and duration of activity increase in patients with renal failure. Dose reduction is required for patients with decreased renal clearance.

Various anticoagulant regimens have been used in the past for the treatment of patients with HITTS with limited effectiveness or even detrimental effects. Warfarin, widely used in the past to replace heparin, has been associated with the development of thrombotic complications, including gangrene, because of severe deficiency of protein C secondary to ongoing thrombosis and further depletion caused by suppression of Vit. K by coumadin.

Low Molecular Weight Heparin are less likely to induce HIT/HITTS than unfractionated heparin, however they cross-react with preformed anti-heparin/PF4 antibodies. The low

molecular weight heparinoid Orgaran has limited cross-reactivity with heparin/PF4 antibodies. Its efficacy for the treatment of HIT/HITTS has been reported in the literature. At present, Orgaran is approved only for thromboprophylaxis in orthopedic surgery.

Argatroban is a synthetic derivative of L-arginine with anticoagulant activity demonstrable *in vitro* and *ex vivo*. Argatroban is a direct inhibitor of free and clot-bound thrombin. The compound reversibly binds to the active site of thrombin blocking all thrombin-induced enzymatic reactions (fibrinogen polymerization, fibrin stabilization by Fact XIII, activation of Fact VIII, V and protein C, platelet activation and aggregation). Argatroban has been evaluated primarily as an anticoagulant for the treatment of patients with heparin-induced thrombocytopenia.

The onset of action of argatroban after intravenous administration is immediate and the anticoagulant effect returns to baseline within 4 hours after discontinuation of administration. The mean terminal half-life of argatroban is approximately 40 minutes.

Argatroban inhibits all thrombin-dependent reactions and prolongs coagulation tests such as PT, TT, aPTT, ACT in a predictable dose-response curve and linear response to steady-state plasma concentrations. Compared to heparin, the anticoagulant effect of argatroban appears to be more constant and predictable with less intersubject variability. Anticoagulation with Argatroban can be monitored *ex vivo* using routine coagulation tests such as aPTT and ACT. Argatroban does not induce antibody formation and does not interact with heparin-induced antibodies.

Argatroban is metabolized primarily in the liver by microsomal P450 enzymes CYP3A4/5. Elimination of radiolabeled argatroban is approximately 65% in feces and approximately 22% in urine within 24 hours.

Drug interaction study with erythromycin did not reveal drug-drug interaction suggesting that CYP3A4/5-mediated metabolism may not be a primary elimination pathway *in vivo*. The concomitant administration of aspirin does not affect the PD of argatroban, however, the additive effect of aspirin on hemostasis is to be expected.

Three studies have assessed the effects of concomitant administration of argatroban and warfarin. The PK and PD of argatroban administered by continuous infusion at a dose of 1.25 ug/kg/min were unaffected by the concomitant administration of a single dose of warfarin. The administration of argatroban by continuous infusion and multiple doses of warfarin increased the sensitivity of the PT/INR compared to warfarin alone. Chromogenic measurements of Fact X were not affected by the administration of argatroban. Vitamin K-dependent factors (Fact X, II, VII, IX, protein C and S) measured by chromogenic assay decreased over time consistent with the expected effect of warfarin. The relationship between INR values with argatroban versus INR values without argatroban is linear and may allow to predict the contribution of warfarin alone to the INR.

A third study, performed to further evaluate the combined effects of argatroban and warfarin on PT/INR in subjects receiving argatroban and warfarin over eight days, also showed that

warfarin and argatroban exerted a combined effect on the INR which fit a linear model based on the dose and plasma concentration of argatroban and the ISI of the thromboplastin reagent used.

These PD studies of drug interaction are clinically relevant to the period of combined anticoagulation with argatroban and warfarin prior to switch to warfarin in patient requiring prolonged anticoagulation.

Argatroban was well tolerated in elderly patients, in renally-impaired patients and in patients with acute coronary syndromes. Administration of argatroban to patients with liver disease showed decreased plasma clearance, higher plasma levels, increased pharmacologic effect and elimination half-life twice that of normal subjects. These results indicate that dose adjustments and frequent monitoring is needed for patients with liver disease.

The dose ranges used in the Phase I and II studies indicated that continuous infusion of argatroban 1.5-2.5 ug/kg/min resulted in steady state aPTT ranging between 44 and 58 seconds. The infusion of 2.0 ug/kg/min provided an aPTT of 1.5x control and the infusion of 10.0 ug/kg/min. prolonged the aPTT at steady state to 3x control.

The clinical development of Argatroban has been directed primarily at its use as an alternative anticoagulant regimen for patients with heparin induced thrombocytopenia. In addition, Phase II studies have evaluated the efficacy and safety of higher doses of Argatroban in coronary intervention procedures and MI. Two Phase III trials have evaluated the efficacy and safety of Argatroban in patients with HIT/HITTS undergoing coronary intervention procedures.

In August 1997, the sponsor submitted NDA 20-883 for the approval of argatroban for anticoagulation in patients with HIT/HITTS. The submission was based on the results of a prospective primary clinical trial (Study ARG-911) of 304 patients and a supportive study (Study ARG-915) of 291 patients with HIT/HITTS treated with argatroban, compared to the data provided by a concurrent historical control. The comparison with a historical control was dictated by ethical concerns that prevented the use of a placebo comparator and by the lack of approved therapy for HIT/HITTS at the time.

The efficacy of argatroban therapy was assessed in terms of reduction of the composite endpoint of death, limb amputation or development of new thromboembolic events compared to that reported for the historical control. Although significant reduction in the incidence of new TEE were observed for HIT and HITTS, and mortality due to TEE were reduced in the treated group, approval was not granted due to the higher overall mortality in the argatroban group. Concern was raised by center diversity, lack of balance between treated and historical control population within each center, and poor comparability between treated and historical controls. The increased mortality was attributed to significant imbalances in patients characteristics, including argatroban treated patients being more seriously ill at baseline.

The sponsor was advised to identify a new appropriate historical control for comparison to the argatroban treated patients or to conduct a new clinical trial comparing argatroban to Refludan in HIT/HITTS patients. The sponsor was also advised to conduct a literature search

of suitable review articles of HIT/HITTS in order to assess the validity of the new historical control in the context of the reported clinical information available at the time.

On August 15, 1999, the sponsor re-submitted NDA 20-883 of argatroban for the indication "as anticoagulant therapy in patients with heparin-induced thrombocytopenia syndrome who, in the opinion of their attending physicians require anticoagulation." In the NDA re-submission, the data from the studies initially included in NDA 20-883 were compared to those of the new historical control.

The historical control proposed by the sponsor and agreed on by the Agency consisted of: 1) eligible patients from a registry of HIT/HITTS cases maintained by Dr. Wallis at Loyola, 2) historical controls from the original historical control group enrolled at sites that also enrolled at least one prospective patient, 3) additional eligible patients enrolled at sites that also enrolled at least three prospective patients. The historical patient population was evaluated for up to 37 days after diagnosis of HIT/HITTS for occurrence of TEE, amputation or death.

The sponsor provided data from a literature search of qualified review articles performed by Dr. Kelton from the Thrombosis Center of Hamilton, Ontario.

The purpose of the literature search was to assess the data from the new historical control in the context of the reported clinical experience with HIT/HITTS. Literature reports were selected based on prespecified requirement, i.e. number of patients, definition of HIT/HITTS, description of outcome events, etc.

The incidence of events for HIT patients reported in the medical literature was 42.3% for the composite endpoint, 36% for TEE, 6% for amputation and 20.2% for all-cause death. The incidence of events for HITTS patients reported in the medical literature was 63.6% for the composite endpoint, 96% for TEE, 5.2% for amputation and 23.9% for all-cause death.

The incidence of events for HIT patients in the historical control was 38.8% for the composite endpoint, 15% for TEE, 2% for amputation and 20.2% for all-cause death. The incidence of events for HITTS patients reported in the medical literature was 63.6% for the composite endpoint, 96% for TEE, 5.2% for amputation and 23.9% for all-cause death.

The outcome events of deaths and composite endpoint for the historical control and literature review were similar. The incidence of new TEE was lower in the historical controls compared to that reported in the literature.

The two clinical trials ARG-911 and -915 are summarized here. In this review, the results of the studies are those presented in the NDA re-submission; the historical control is the new, revised historical control agreed on at a meeting on July 14, 1998 and as further revised on September 16, 1998.

Data from the literature survey are also included for comparison.

Study ARG-911: “An open-label Study of Novastan (brand of argatroban) in patients with Heparin-Induced Thrombocytopenia (HIT) or Heparin-Induced Thrombocytopenis with Thrombosis (HITTS)”.

Summary of the Study Design: The study was multicenter and historically controlled. The objectives of the study were to assess the efficacy and safety of argatroban as a prophylactic anticoagulant for prevention of thrombosis in patients with HIT and as an anticoagulant for the treatment of thrombosis in patients with HITTS.

The study was historically controlled because ethical consideration made the randomized placebo-controlled design unacceptable. At the time of the study, no treatment was available for HIT/HITTS to allow an active control design.

The historical control included 193 patients (147 HIT and 46 HITTS patients).

The study period of the argatroban-treated patients included a pre-treatment period of up to 1 week, a treatment period of up to 14 days and a follow-up period up to day 30 +/- 7 days. A total of 304 prospective patients were enrolled in the study.

Argatroban was administered as a continuous infusion at the initial dose of 2ug/kg/min to be titrated up to a maximum dose of 10ug/kg/min. The effect of Argatroban was monitored by the aPTT which was aimed at 1.5-3.0 x baseline and not higher than 100 seconds. Patients could continue treatment for a maximum of 14 days or less if the underlying thrombosis or risk of thrombosis had resolved or adequate anticoagulation could be provided and had been achieved with other anticoagulant regimen (warfarin).

The primary efficacy outcome of argatroban therapy was assessed in terms of occurrence of one or more of the composite outcome of new thromboembolic events (TEE), amputation, or death from all causes within 37 days from time of initiation of argatroban therapy. Secondary endpoint was time to occurrence of all cause death, amputation or new TEEs. Efficacy analyses were conducted separately for the HIT and HITTS patients populations in both treated and historical control patients.

The primary efficacy endpoint was analyzed by both categorical and time-to-event method. Time-to-event curves were generated using Kaplan-Meier estimates and compared using the Log-rank test.

The individual components of the composite endpoint were compared between groups using categorical analysis.

Hazard ratio and 95% CI were estimated by regression analysis. In addition, categorical and time-to-event analyses for the composite endpoint were conducted on a cumulative basis for study day intervals 0-7, 0-14, 1-21, 0-37 on the ITT population.

The efficacy analyses were performed on the Intent-To-Treat (ITT) population that included all treated patients and all historical controls, on the Evaluable population that included all treated patients assessed by the DSMB as having the diagnosis of HIT or HITTS and all historical controls, and on the Test-positive population that included all treated patients and historical controls with positive tests for heparin-induced thrombocytopenia.

The primary safety variable was the comparative incidence of major bleeding.

Results of the Study: Statistically significant differences in baseline characteristics were observed for age in both HIT and HITTS groups (historical controls mean age 66 years versus treated patients mean age 61 years), and for gender in the HIT group (more females in the control group and more males in the treated group); however, the clinical relevance of such imbalance is unclear.

Platelet counts were lower in both HIT and HITTS treated groups compared to the historical controls. A total of 21 patients (13%) of treated patients in the HIT group had not received heparin within 6 weeks prior to argatroban therapy.

Comparison of baseline pre-treatment medical conditions indicated significant differences in favor of the historical controls for most categories.

The mean (\pm SD) duration of therapy was 5.3 ± 0.3 days and 5.9 ± 0.2 days for HIT and HITTS respectively. Overall, 254 of the 304 enrolled patients (83%) received argatroban until resolution of underlying condition, appropriate anticoagulation with warfarin was provided or to the maximum duration of 14 days.

Efficacy Results: The sponsor's results of the categorical analysis of the primary efficacy endpoint and of the LOG-rank test on the time-to-first-event for the composite endpoint for the HIT and HITTS groups are summarized in the following tables reproduced from the statistical review by Dr. Wen-Jen Chen.

Table 2.2.2.1 (Sponsor's) Categorical Analysis Results on the Composite Endpoint and Its Individual Component Using ITT Patient Population

Parameter	HIT				HITTS				
	Historical Control		Argatroban		Odds Ratio (95% CI)	Historical Control		Argatroban	
	N (%)	N (%)	P-value ^a	N (%)		N (%)	P-value	Odds Ratio (95% CI)	
Total Patients	147	160			46	144			
Death (All Causes) ^b	32 (21.8)	27 (16.9)	0.311		13 (28.3)	26 (18.1)	0.146		
Amputation (all causes) ^b	3 (2.0)	3 (1.9)	1.00		4 (8.7)	16 (11.1)	0.787		
New Thrombosis ^b	22 (15.0)	11 (6.9)	0.027 [*]		9 (19.6)	21 (14.6)	0.486		
Composite Endpoint	57 (38.8)	41 (25.6)	0.014 [*]	1.84 (1.13, 2.99)	26 (56.5)	63 (43.8)	0.131	1.67 (0.86, 3.26)	

Source: Sponsor's Table 20 in volume 74; *: Significant under significance level of 0.05;

a: Based on the 2-sided Fisher's exact test for the individual components and on the Chi-square test for the composite endpoint;

b: Reported only if it was most severe outcome (severity ranking: death>amputation>new thrombosis).

Table 2.2.2.2 Results of logrank tests on the time-to-first-event for the composite endpoint using ITT population

Parameter	HIT				HITTS			
	NO. of Patients		Logrank P-value	Hazard Ratio (95% CI)	NO. of Patients		Logrank P-value	Hazard Ratio (95% CI)
	Arga. ¹	HC. ²			Arga. ¹	HC. ²		
Argatroban vs. Historical	160	147	0.007 [*]	1.725 (1.15-2.58)	144	46	0.018 [*]	1.71 (1.08-2.70)

1: argatroban; 2: Historical Control; *: significant under significance level of 0.05.

(1.13, 2.99)

(0.86, 3.26)

Source: Sponsor's Table 20 in volume 74; *: Significant under significance level of 0.05;

a: Based on the 2-sided Fisher's exact test for the individual components and on the Chi-square test for the composite endpoint;

For the HIT population, the incidence of the composite endpoint was significantly lower in the argatroban treated patients. Of the components of the composite endpoint distributed by most severe outcome, new TEE were significantly less in the argatroban treated patients; deaths were numerically less in the treated group, but the difference was not statistically significant; the incidence of amputation was similar in both groups.

For the HITTS population, no statistically significant differences in incidence of composite endpoints or of its components were observed between the treated and historical control groups.

Log-rank test for secondary efficacy endpoint of time to first event of the composite endpoint for both HIT and HITTS populations showed statistically significant differences between treated and control groups in favor of argatroban treatment.

Secondary efficacy of argatroban therapy (adequate anticoagulation and resolution of thrombocytopenia) was demonstrated. A total of 83% and 94% HIT and HITTS patients respectively achieved aPTT > 1.5x baseline and most of them within 4-5 hours. Platelet counts improved by day 3 in the treated patients whereas an initial decrease in platelet counts was observed in the historical controls for few days after discontinuation of heparin.

The following additional analyses were performed by the Agency's statistical reviewer on the ITT database of HIT and HITTS populations: 1) effect of baseline variables on treatment efficacy, 2) center consistency, 3) subgroup analysis for internal consistency.

For the HIT population, the results indicate in general the efficacy of argatroban was not affected by baseline disease and demographic variables.

The efficacy of argatroban differed in patients who had or had not received heparin within 6 weeks from enrollment. No events were reported in patients with no recent exposure to heparin, however, patients with "latent HIT" were eligible for inclusion in the study for use of argatroban for thromboprophylaxis.

A study by center interaction was observed for Center A, however, a statistically significant difference in patient distribution among centers between treated and control population was found for both HIT and HITTS groups. The significance of these imbalances is unclear given the complexity of the disease, overlap of HIT and HITTS, and the unavoidable patient variability in both treated and control groups.

Safety Results: Overall, no significant differences in the incidence of major or minor bleeding were observed between the treated and the historical control groups.

Statistically significant differences in frequency of adverse events occurring in more than 5% of patients between treated and control groups in both HIT and HITTS populations were observed, however no consistent patterns were detected in HIT or HITTS populations for AEs involving the same system.

Study ARG-915: "An open-label clinical study of Novastan (brand of argatroban) in patients with Heparin-induced thrombocytopenia (HIT)/heparin-induced thrombocytopenia and thrombosis syndrome (HITTS)."

The objective of this study was to evaluate the efficacy and safety of argatroban in patients with HIT/HITTS requiring anticoagulation therapy and to allow continued availability of argatroban to patients without pre-defined sample-size limitations. The study was similar in design to study ARG-911 except for allowing patients who had participated in study ARG-911, and patients who had already participated in study ARG-915 as well, to be re-enrolled in this open-label study. A total of 291 patients, including 27 repeat patients, were enrolled in the study between November 1996 and October 1997 when enrollment in the study was closed. Enrollment of patients with HIT/HITTS to treatment with argatroban was however continued under the extension Study ARG-915X.

Study ARG-915 was initially designed as an open-label observational study with no pre-specified comparison to the historical control and no pre-established study size. In October 1997, because of the large number of patients entered in the study, the sponsor decided to carry out a comparison of efficacy and safety results to that of the historical control selected for Study ARG-911. A total of 264 patients (125 HIT and 139 HITTS patients) were thus compared to the historical control. Repeat patients were excluded from this comparison. For both HIT and HITTS groups, the efficacy and safety analyses were performed on the ITT population.

No major discrepancies were noted between treated and control patients for demographic characteristics; no comparison was made for baseline medical parameters.

The sponsor's categorical analysis of the composite endpoints and of its individual components the Log-rank test on time to first event for the composite endpoint are summarized in the following tables reproduced from the statistical review.

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Table 3.2.2.1 (Sponsor's) Categorical Analysis Results on the Composite Endpoint and Its Individual Component Using ITT Patient Population

Parameter	HIT				HITTS				
	Historical Control		Argatroban		Odds Ratio (95% CI)	Historical Control		Argatroban	
	N (%)	N (%)	N (%)	N (%)		P-value*	P-value*	Odds Ratio (95% CI)	
Total Patients	147	125				46	139		
Death (All Causes) ^b	32 (21.8)	21 (16.8)	0.357			13 (28.3)	35 (25.2)	0.700	
Amputation (all causes) ^b	3 (2.0)	6 (4.8)	0.309			4 (8.7)	16 (11.5)	0.786	
New Thrombosis ^b	22 (15.0)	5 (4.0)	0.004 [*]			9 (19.6)	6 (4.3)	0.003 [*]	
Composite Endpoint	57 (38.8)	32 (25.6)	0.021 [*]	1.84 (1.09, 3.099)		26 (56.5)	57 (41.0)	0.067	1.87 (0.95, 3.67)

Source: Sponsor's Table 8 in Volume 7B. *: Significant under significance level of 0.05;

a: Based on the 2-sided Fisher's exact test for the individual components and on the Chi-square test for the composite endpoint.

b: Reported only if most severe outcome (severity ranking: death>amputation>new thrombosis).

Table 3.2.2.2 (Sponsor's) Results of Logrank tests on the time-to-first-event for the composite endpoint using ITT population

Parameter	HIT				HITTS			
	NO. of Patients		Logrank P-value	Hazard Ratio (95% CI)	NO. of Patients		Logrank P-value	Hazard Ratio (95% CI)
	Arga. ¹	HC. ²			Arga. ¹	HC. ²		
Argatroban vs. Historical	125	147	0.0217 [*]	1.646 (1.07-2.54)	139	46	0.0124 [*]	1.78 (1.12-2.83)

1: argatroban; 2: Historical Control; *: significant under significance level of 0.05.

Only for the HIT group, the incidence of the composite endpoint was statistically significantly lower in the treated group compared to the historical control. For both HIT and HITTS groups, the incidence of new thrombosis as the most severe outcome was significantly lower in the treated group compared to the historical controls.

The results of the log-rank tests on time to first event for the composite endpoint indicated a statistically significant difference in favor of argatroban treatment for both HIT and HITTS populations.

As in Study ARG-911, argatroban resulted in adequate anticoagulation and resolution of thrombocytopenia.

The incidence of bleeding (overall, major and minor) were similar in the treated and control groups in both HIT and HITTS populations. The bleeding complications were also similar to that reported in study ARG-911.

Comments and Conclusions

The efficacy and safety of argatroban was demonstrated in two clinical trials of HIT/HITTS patients when compared to a specified historical control and a literature-derived historical control.

The use of historical controls to assess the efficacy and safety of new drugs of therapeutic interventions is always of concern. Significant limitations of historical control studies are lack of accurate, uniform and complete data collection, changes in diagnostic criteria for a given disease, new therapies and better supportive measures. However, because of the severity of the HIT/HITTS indication, a randomized placebo controlled clinical trial was unacceptable for ethical considerations. An active control study was not possible because no approved regimen was yet available when the studies were performed.

The results of the two studies indicate that argatroban treatment significantly reduced the risk of new TEE and of the composite endpoint in the HIT population. The efficacy of argatroban was demonstrated when the results of the clinical trials were compared to the historical control and when assessed in the context of the available database from the medical literature.

Argatroban appears to be effective in preventing or reducing the risk of TEE in patients with HIT who are at risk of progressing from thrombocytopenia to thrombosis and in patients with "latent HIT" who are at risk of complications if re-exposed to heparin or LMWH.

Occurrence of new thrombosis was also significantly reduced in HITTS patients treated with argatroban.

Mortality from all cause was numerically reduced in HIT patients by treatment with argatroban. Mortality was not affected by treatment in the HITTS group most likely because it was determined by the severity of the underlying conditions and by the grave impact of the thrombotic complications in very ill patients. Mortality could seldom be attributed solely to TEE, however, this determination was confounded by the fact that death was often the result of multi-organ failure.

Amputation rates were not affected by treatment because this outcome represented the irreversible consequence of thrombotic complications and ischemic process.

The sponsor's analyses of the combined HIT and HITTS populations shows statistical significance in both ARG-911 and -915 studies (p-value not corrected for multiple analyses). The data are summarized in the following table reproduced from the sponsor's Summary of Clinical Data

	HIT					HITTS				
	Historical Control		Argatroban		p-value ^a	Historical Control		Argatroban		p-value ^a
	N	%	N	%		N	%	N	%	
Total Number of Patients	147		125			46		139		
Death (all causes) ^b	32	(21.8)	21	(16.8)	0.357	13	(28.3)	35	(25.2)	0.700
Amputation (all causes) ^b	3	(2.0)	6	(4.8)	0.309	4	(8.7)	16	(11.5)	0.786
New Thrombosis ^b	22	(15.0)	6	(4.0)	0.004	9	(19.6)	8	(4.3)	0.003

^a Based on the Fisher's exact test for the individual components.
^b Reported only if most severe outcome (severity ranking: death>amputation>new thrombosis); patients may have had multiple outcomes.
 Reference Documentation Section 8D, Vol. 6.32 pg.001.

The efficacy of argatroban was less pronounced in HITTS probably because of the overall poor prognosis and irreversible pathology associated with thrombosis. One can speculate that the TEE of HITTS carry a worse prognosis than thrombotic events in general because of their immune-mediated pathogenesis. It is possible that once initiated, the immune thrombogenesis process is unlikely reversible.

It must be noted that the distinction between HIT and HITTS is only descriptive. In fact, the two conditions may represent progressive manifestations of the same pathogenetic mechanism. Whether HITTS is the result of a stronger immune process or whether is due to additional and still undefined risk factors is unclear at present. Older age, earlier onset of thrombocytopenia and degree of platelet reduction appear to be unfavorable risk factors.

No increase in severe or major bleeding was reported. No significant or unexpected adverse events were observed in the study population.

However, evaluation of cause of death has shown more cardiac deaths in the argatroban treated patients compared to the historical controls and one patient being discontinued from the study possibly because of arrhythmia. The significance of these observations is unclear at present in the absence of information regarding concomitant medications and given the severity of the underlying medical condition.

Argatroban exhibit many favorable pharmacologic features. It is a direct antithrombin with rapid onset of action and reasonably short duration of anticoagulant effect. The effect of argatroban is not dependent of cofactors therefore it has a more predictable dose-response curve that heparin. The compound has rapid elimination not dependent on renal excretion. Argatroban does not interact with heparin/PF4 antibodies and is not itself antigenic. Argatroban therapy can be monitored with routine tests such as aPTT and ACT.

Sufficient information has been generated to allow dosing of argatroban for cardiac interventions in HIT/HITTS patients. Repeat administration of argatroban has been carried out in about 40 patients with no adverse events.

It is therefore recommended that argatroban be approved for "treatment of patients with heparin-induced thrombocytopenia who require anticoagulant therapy".

The following recommendations should be conveyed to the sponsor:

The sponsor should address the use of argatroban in the pediatric population with HIT/HITTS.

The sponsor should assess the effect of argatroban on cardiac conduction. The sponsor should commit to Phase 4 studies to conduct *in vitro* electrophysiology tests and additional drug interactions, and to obtain ECG Holter monitoring in a selected group of patients receiving argatroban.

The sponsor should continue the assessment of the efficacy and safety of argatroban for anticoagulation for cardiac procedures and should consider initiating studies of argatroban for hemodialysis.

Labeling recommendations will be addressed as labeling review.

/S/

Lilia Talarico, M.D.

cc:

NDA 20-883

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HFD-180/LTalarico

HFD-181/PM

HFD-180/JChoudary

HFD-180/LZhou

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MEMORANDUM

Department of Health & Human Services

Public Health Services
 Food and Drug Administration
 Center for Drug Evaluation and Research
 Division of Testing and Applied Analytical Development
 Laurel, MD 20708

Date 01/19/00
 From: Sylvester West, Chemist, HFD-920
 Subject: Methods Validation for NDA No. 20-883
 To: Ali AL-Hakim, Ph.D., Reviewing Chemist, HFD-180
 Through: Don Cox, HFD-920



Texas Biotechnology Corporation submitted for review, evaluation and testing a Method Validation Package (MVP) application and several exhibit samples that consisted of one lot of Novastatin Injection Concentrate solution, Argatroban Reference Standard No. 2 and two related substances.

The exhibited lot was analyzed as near as possible to the test descriptions in the MVP. All of the tests were performed after the applicant's system suitability requirements for the method were met. Even though the calculations used to determine system suitability were based on questionable practices, the system suitability specification tests were followed. The test results obtained for the theoretical plates and for the tailing factor in the assay of potency and related substances appear not to be valid because unresolved peaks were measured instead of a single peak. In ~~_____~~ the tailing factor of an eluting band is typically associated with the bonding dynamics of the stationary phase rather than with the merger of two peaks. In fact, authors of notable distinction in ~~_____~~ (Snyder, Kirkland, *Introduction To Modern Liquid Chromatography*, 1979, page 807) refer to the condition as 'apparent band tailing' or 'pseudo tailing'. Theoretical plates are by convention measured on a single peak. Also, it is observed in the MVP that the applicant casually uses the relative retention ratio (called selectivity, separation factor) to measure the relative retention time.

Characterization of the single preparation required three separate ~~_____~~ analytical procedures. The time run duration of one injection in one of the procedures exceeded two hours. Assay of potency and identity, determination of related substances and measurement of the ratio of the stereoisomers were tests that constituted the analysis of the exhibit lot.

All the ~~_____~~ methods appear to have originated from other methods after an evaluation by ~~_____~~. It seems that the revisions were adopted to align the methodologies to the USP format.

In conclusion, the methods are deemed suitable except for the system suitability calculations when they were performed on the columns prescribed by the MVP. Extrapolation to the usual designated equivalent columns in uncomplicated analyses may not be a suitable substitute. An example of this problem was encountered in the validation method for the assay for potency. It was suggested that a Symmetry column should be a suitable alternative for the applicant's recommended Lichrosorb column as both had similar carbon loads. In practice, however, the retention times of the stereoisomers, Type I and Type II, using the Symmetry column were split with retention times of 28.7 and 30.4 minutes, respectively. As the method predicts and a typical MVP chromatogram shows, the Lichrosorb column produced poorly resolved stereoisomers with a common retention time of about 16.6 minutes.

The test results of the ~~_____~~ assays of Novastatin Injection Concentrate solutions are included in the validation report.

~~_____~~
 Sylvester West

1 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

MEMORANDUM

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

DATE: January 6, 2000

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

SUBJECT: NDA 20,883 (NOVASTAN/Argotroban) -
Preclinical Portions of the Labeling

TO: NDA 20,883

The following portions of the sponsor's "unannotated" draft labeling dated August 13, 1999 should be replaced or expanded with the accompanying revisions/additions.

1. "PRECAUTIONS"
 - a. "Carcinogenesis, Mutagenesis, Impairment of Fertility" - on page 12 of the sponsor's 8/13/99 unannotated draft.
 - b. "Pregnancy Category B" - on page 12 of the sponsor's 8/13/99 unannotated draft.
2. "OVERDOSAGE" - on pages 15 and 16 of the sponsor's 8/13/99 unannotated draft.

1. PRECAUTIONS

a. Carcinogenesis, Mutagenesis, Impairment of Fertility

"Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term studies in animals have been performed to evaluate the carcinogenic potential of argotroban.

Argotroban was not genotoxic in the Ames test, the Chinese hamster ovarian cell (CHO/HGPRT) forward mutation test, the Chinese hamster lung fibroblast chromosome aberration test, the rat hepatocyte- and WI-38 human fetal lung cell unscheduled DNA synthesis (UDS) tests, or the mouse micronucleus test.

Argotroban at i.v. doses up to 27 mg/kg/day (0.3 times the recommended maximum human dose based on body surface area) was found to have no effect on fertility and reproductive performance of male and female rats.

b. Pregnancy Category B

"Pregnancy. Teratogenic Effects. Pregnancy Category B.

Teratology studies have been performed in rats at i.v. doses up to 27 mg/kg/day (0.3 times the recommended maximum human dose based on body surface area) and rabbits at i.v. doses up to 10.8 mg/kg/day (0.2 times the recommended maximum human dose based on body surface area) and have revealed no evidence of impaired fertility or harm to the fetus due to argotroban. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

2. OVERDOSAGE (to be added on page 16)

"OVERDOSAGE

Single i.v. doses of argotroban at 200, 124, 150 and 200 mg/kg were lethal to mice, rats, rabbits and dogs, respectively. The symptoms of acute toxicity were loss of righting reflex, tremors, clonic convulsions, paralysis of hind limbs and coma.

/S/

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

cc:

NDA

HFD-180

HFD-181/CSO, Ms. DuBeau

HFD-180/Dr. Choudary

JBC/hw/1/6/00

MEMORANDUM

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

DATE: May 4, 1998

FROM: Dr. Lilia Talarico, Division Director, Division of
Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Novastan® (argatroban) Injection, NDA 20-883

TO: Dr. Paula Botstein, Acting Director, Office of Drug Evaluation and
Research III, HFD-103

Heparin-induced thrombocytopenia (HIT) is an immune-mediated adverse drug reaction characterized by in vivo platelet activation, thrombocytopenia and high risk of thromboembolic complications. HIT occurs with a frequency of about 3% in patients receiving heparin for longer than 5 days. Next to bleeding, HIT is the most important adverse reaction to heparin.

Contrary to most drug-induced immune thrombocytopenias which are characterized by severe thrombocytopenia and bleeding, the reduction in platelet count of HIT is usually mild and bleeding manifestations are rare. Much more serious are the thrombotic manifestations that occur as result of platelet activation and development of a prothrombotic state. Approximately 1% of patients with HIT experience new thrombotic complications after the initiation of heparin. This complication has been designated as HITTS (Heparin-induced thrombocytopenia with thrombosis syndrome). Both venous and arterial thromboses occur and can result in organ failure, limb amputation, or death.

The treatment of HIT consists in the discontinuation of heparin administration. Alternative options for anticoagulant treatment of the initial thrombosis for which heparin therapy had been instituted or of thrombosis that occur during the heparin administration, have included defibrinating snake venoms, heparinoid Orgaran, synthetic antithrombins and recombinant hirudin. A recombinant hirudin, Repludan has recently been approved for HIT patients requiring anticoagulant therapy.

Argatroban is a synthetic, direct antithrombin derived from L-arginine. Argatroban selectively binds to and inhibits the active site of thrombin. This effect can be assessed by a dose-related prolongation of APTT, PT, ACT and TT. The half life of Argatroban is about 54 minutes and is not affected by renal failure. Argatroban is metabolized by the liver and is not excreted by the kidney. Argatroban does not cross-react with anti-heparin antibodies and is not antigenic.

The anti-thrombotic efficacy of Argatroban has been demonstrated in various animal models of thrombosis. Argatroban has been investigated in clinical trials in acute coronary syndromes and in patients with HIT. Argatroban is approved in Japan since 1990 for the treatment of peripheral vascular diseases and since 1996 for hemodialysis, acute thrombotic stroke, and for anticoagulant therapy in patients with AT-III deficiency. Several thousands of patients have received Argatroban.

The clinical evaluation of Argatroban as alternative anticoagulant/antithrombotic therapy for patients with HIT or HITTS was initiated in 1988. On 8-15-1997, the sponsor submitted NDA 20-883 for the approval of Argatroban as "Anticoagulant therapy in patients with heparin-induced thrombocytopenia." In support of this indication, a single, multi center, historically-controlled, open-label, prospective study of 304 patients with HIT or HITTS was submitted (Study ARG-911). The efficacy and safety data from this prospective studies were compared to an

historical control constructed from retrospective cases of HIT/HITTS provided from investigators participating in the ARG-911 study. A total of 103 study sites participated in study ARG-911, of these sites, four contributed more than 10 patients. One Canadian investigator (Warkentin) provided approximately 50% of the historical controls from three sites but no Argatroban-treated patients.

After completion of study ARG-911, 271 additional patients with HIT/HITTS were enrolled in study ARG-915, an open-label, compassionate use, multi center extension study.

In both studies, Argatroban was administered as a continuous infusion at the dose of 2-10 mcg/kg/min (dose adjusted to APTT of 1.5 to 3.0 times baseline). Treatment was continued until clinical resolution of thrombosis and switch to other anticoagulant regimen (ASA, Warfarin), or for up to 14 days.

Primary efficacy endpoints were new thrombotic events (TE), amputations, or death. Two composite endpoints were analyzed: the overall composite outcome endpoint which included the number of patients who experienced one or more of the events (new TE, amputation or death due to any cause) and the thrombotic composite outcome endpoint which included all patients who experienced new TE, death due to thrombosis and amputation due to ischemic complications of HIT or HITTS. All statistical analyses were performed on the intent-to-treat (ITT) populations; the incidence rates for new TE, limb amputations due to ischemia, all deaths and deaths due to thrombosis, overall and thrombotic composite outcome were compared between the Argatroban-treated and the historical control groups. Secondary efficacy analyses included comparison of survival curves for outcome events between Argatroban-treated patients and historical controls.

The results of study ARG-911 are summarized in the following table.

Primary Efficacy Outcomes for Study ARG-911

Efficacy Outcomes	HIT			HITTS		
	Hist Ctrl 108	Argatro 160	P-value*	Hist Ctrl 109	Argatro 144	pvalue*
New Thromboses	25 (23%)	10 (6%)	0.0001	45 (41%)	27 (19%)	0.0001
Amputation	4 (4%)	4 (3%)	N. S.	13 (12%)	18 (13%)	N. S.
All-cause Death	12 (11%)	29 (18%)	0.124	16 (15%)	26 (18%)	0.500
Overall Composite	36 (33%)	43 (27%)	0.276	59 (54%)	62 (43%)	0.099

* two-sided Fisher's Exact Test

Adapted from Tables 15 and 16, vol. 105, pp. 107-8

A statistically significant difference in favor of Argatroban was observed for the incidence of new thromboses in both HIT and HITTS patients, however, the incidence of all cause deaths was numerically higher in the Argatroban groups compared to the historical controls in both HIT and HITTS patients. A total of 14% and 27% of deaths in Argatroban-treated HIT and HITTS patients, respectively, occurred early, namely during the treatment phase or up to 14 days, 67% and 75% of deaths in HIT and HITTS patients, respectively, in the historical control occurred during an equivalent period of time.

The sponsor re-analyzed the deaths according to the classification of death due to thrombosis or to the underlying diseases. In this analysis significantly more deaths due to thrombosis were found in the historical controls compared to the Argatroban-treated patients in both HIT and HITTS groups.

The results of the sponsor's analysis of deaths are shown in the following table.

Sponsor's Subclassification of Deaths

Cause of Death	HIT		P-value*	HITTS		pvalue*
	Control 108	Argatroban 160		Control 109	Argatroban 144	
Thrombosis	4 (4%)	0 (0%)	0.026	8 (7%)	1 (1%)	0.006
Treatment Emergent	0 (0%)	2 (1%)	0.517	0 (0%)	1 (1%)	N. S.
Underlying Disease	8 (7%)	27 (17%)	0.027	8 (7%)	24 (17%)	0.035

* two-sided Fisher's Exact Test. Adapted from Tables 15 and 16, vol. 105, pp. 107-8

The CRFs of all deaths were reviewed by the MO (Dr. Sizer) and each case was classified as due to TE or to underlying condition. The results are summarized in the following table.

Medical Reviewer's Subclassification of Deaths

Cause of Death	HIT		HITTS	
	Control N=108	Argatroban N=160	Control N=109	Argatroban N=144
All Causes	12 (11%)	29 (18%)	16 (15%)	26 (18%)
Thrombosis	5 (5%)	7 (4%)	8 (7%)	10 (7%)
Other causes	7 (6%)	22 (14%)	8 (7%)	16 (11%)

No significant difference was observed for mortality due to thrombosis between treated and historical control patients in both HIT and HITTS. The higher mortality rates due to underlying diseases reported for the Argatroban-treated patients were attributed, by the sponsor, to the significant differences in patients' health status, with Argatroban-treated patients being substantially more compromised compared to the historical controls.

One reason for the imbalance between the historical and treated groups was the selection of historical control which excluded patients with serious underlying conditions such as cancer, sepsis, renal failure, multi-organ failure, etc.

The following table (Table 11, vol. 105, p. 97) summarizes the imbalance between the groups.

Summary of Medical/Surgical/Invasive Procedure History by Medical History

Medical History	HIT			HITTS		
	Control N (%)	Argatroban N (%)	P-value	Control N (%)	Argatroban N (%)	P-value
Number of Patients	108	160		109	144	
Cancer	10 (9)	29 (18)	0.052	17 (17)	25 (17)	0.736
Renal Failure	14 (13)	46 (29)	0.003	6 (6)	37 (26)	<0.001
Hepatic Failure	5 (5)	15 (9)	0.164	1 (1)	15 (10)	0.001
Diabetes	28 (26)	45 (28)	0.780	27 (25)	50 (35)	0.099
Sepsis	6 (6)	19 (12)	0.090	3 (3)	17 (12)	0.009
Lupus Erythematous	2 (2)	6 (4)	0.481	1 (1)	8 (6)	0.082
ARDS	19 (18)	29 (18)	1.00	12 (11)	29 (20)	0.059
Ongoing Procedures						
Hemodialysis	4 (4)	22 (14)	0.006	1 (1)	10 (7)	0.026
Circ.Assist Device	7 (7)	19 (12)	0.206	2 (2)	19 (13)	0.001
On Respirator	13 (12)	9 (6)	0.071	9 (8)	11 (8)	1.00
Previous Surgery						
CABG	39 (36)	46 (29)	0.229	26 (24)	71 (50)	<0.001

At least three of the above conditions, (cancer, renal impairment, ARDS), were, in fact, determined from stepwise regression to be statistically significant predictors of all cause mortality. When the incidence of the overall composite endpoint and that of all cause mortality in the Argatroban-treated HIT or HITTS patients was adjusted for the above covariates using the logistic regression model, a statistically significant effect on overall composite endpoint and a positive (although not significant) effect on all cause mortality were observed for Argatroban-treated HITTS patients. The results were inconsistent in the Argatroban-treated HIT patient.

On 2-9-1998, subsequent to the NDA submission, the sponsor submitted the data from the first 174 of the 271 patients enrolled in Study ARG-915. The safety and efficacy data from this patient population were compared to the same historical control used for study ARG-911. Because of the limitations of study, the primary focus of the analyses of the data from study ARG-915 was not to assess the efficacy of Argatroban therapy, rather to further investigate the incidence and cause of death.

The primary efficacy outcome results from study ARG-915 are summarized in the following table.

Primary Efficacy Outcomes for Study ARG-915

Efficacy Outcomes	HIT			HITTS		
	Control	Argatroban	P-value*	Control	Argatroban	P-value*
New Thromboses	25(23%)	3(4%)	0.0001	45(41%)	8(9%)	0.0001
Amputation	4(4%)	6(7%)	0.340	13(12%)	13(15%)	0.531
All-cause Death	12(11%)	16(19%)	0.152	16(15%)	23(26%)	0.072
Overall Composite	36(33%)	21(25%)	0.207	59(54%)	33(37%)	0.031

Two-sided Fisher's E Tt. Adapted from Sponsor's Tables 11/ 12, vol. 12.1, pp. 31-2, and information from vol. 12.7, p.297

Contrary to study ARG-911 where a significant imbalance for risk factors existed in the Argatroban-treated HIT and HITTS patients compared to the historical control, the patient populations in study ARG-915 were more similar. A summary of patient medical/ surgical/ invasive procedure history by medical history, is shown below. (Table 8, vol. 12.1, p. 23)

Summary of Medical/Surgical/Invasive Procedure History by Medical History

Medical History	HIT		P-value	HITTS		P-value
	Control N (%)	Argatroban N (%)		Control N (%)	Argatroban N (%)	
Total Number of Patients	108	85		109	89	
Cancer	10 (9)	8 (9)	1.00	17 (17)	3 (3)	0.004
Renal Failure	14 (13)	22 (26)	0.003	6 (5)	15 (17)	0.011
Hepatic Failure	5 (5)	2 (2)	0.468	1 (1)	6 (7)	0.047
Diabetes	28 (26)	19 (22)	0.615	27 (25)	33 (37)	0.065
Sepsis	6 (6)	9 (11)	0.279	3 (2)	7 (8)	0.116
Lupus Erythematous	2 (2)	0 (0)	0.505	1 (1)	2 (2)	0.589
Resp. Distress Syndrome	19 (18)	7 (8)	0.088	12 (11)	8 (9)	0.813
Ongoing Procedures						
Hemodialysis	4 (4)	2 (2)	0.696	1 (1)	0 (0)	1.000
Circ.Assist Device	7 (7)	13 (15)	0.058	2 (2)	15 (17)	<0.001
On Respirator	13 (12)	0 (0)	<0.001	9 (8)	2 (2)	0.116
Previous Surgery						
Previous CABG	39 (36)	27 (32)	0.229	26 (24)	45 (50)	<0.001

A statistically significant imbalance for renal failure was observed between Argatroban-treated HIT and HITTS patients and historical controls; other prognostic factors occurred with greater frequency in any one of the groups including the historical controls. Therefore, the attribution of the higher mortality rates in the Argatroban-treated patients to the greater frequency of concomitant severe medical conditions in the treated groups compared to historical controls was not supported by the findings in study ARG-915.

The primary causes of death in both Argatroban-treated and historical control patients were indeed thromboses and organ system failure. The most severe adverse events reported in the Argatroban-treated patients were thromboses and hemorrhage. No statistically significant difference in rates of major bleeding were seen between Argatroban-treated patients and historical control for both HIT and HITTS groups. No deaths were attributed to Argatroban and no other severe individual treatment-emergent adverse event occurred more often in Argatroban-treated patients. No trends were observed to indicate Argatroban toxicity.

Our concerns for mortality results from studies ARG-911 and -915 were conveyed to the sponsor on March 26, 1998 in a teleconference.

On April, 9, 1998, in replay, the sponsor submitted comments from one of the principal investigators for study ARG-911, Dr. B.Lewis and from a consultant, Dr. J.G.Kelton. Both Dr. Lewis and Kelton emphasized the limitations of the historical control used for study ARG-911 and ARG-915 to reflect the true incidence of death in HIT and HITTS patients. Dr. Lewis also indicates that a registry (Loyola HIT Registry) was formed for the years 1992-96. This registry of 114 patients reports

mortality rate of 34%. These data have not been reviewed.

In conclusion, a significant reduction in incidence of new TE was observed in both HIT and HITTS Argatroban-treated patients in bot studies. Overall mortality rates were higher for the Argatroban-treated patients compared to the historical control in both studies. The mortality rates attributed to thrombotic events by our assessment were similar for the Argatroban-treated patients and the historical controls in both HIT and HITTS patients. Since the data submitted in the NDA indicate that the efficacy of Argatroban in reducing the incidence of new thrombotic events did not result in reduction in overall mortality nor of mortality due to thrombosis according to our evaluation, approval of Argatroban for anticoagulation of patients with heparin-induced thrombocytopenia cannot be recommended.

The sponsor should be advised to analyze the data from an appropriate historical control or from the Loyola HIT Registry as these patients may represent a more valid historical control group since they were collected at the same time as the patients enrolled in study ARG-911.

The sponsor should be advised to conduct a double-blind, randomized, multicenter study comparing argatroban to a currently approved therapy for HIT/HITTS in patients who need anticoagulation.

The sponsor should also be advised to pursue the evaluation of Argatroban as alternative to heparin in HIT-patients undergoing cardiopulmonary bypass surgery or renal dialysis.


Lilia Talarico, M.D.

cc:
NDA 20-883
HFD-180/Div. files
HFD-180/Sizer
HFD-180/Talarico
HFD-720/Sankoh
HFD-180/DuBeau
JD/5/4/98/

Memo to: Ms Julieann DuBeau
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
FDA CDER
FAX No. 301-443-9285

From: Gary Knappenberger
Senior Director, Clinical and Regulatory Affairs
Texas Biotechnology Corporation

Subject: NOVA[®]STAN[®] (argatroban)

As I mentioned over the telephone, TBC has two questions which we would like to address today, July 15 with Dr. Talarico and yourself. These questions were raised by our potential corporate development and marketing partner, SmithKline Beecham. Because of the timing of our discussions with them, these issues were not raised by them until after our pre-NDA meeting with you on May 21st.

The first question relates to our Pre-NDA meeting and the outcome of the meeting. One of the objectives of the meeting was to obtain Agency feedback on whether there is sufficient data available to submit an NDA based on the single pivotal study, ARG-911. Because we are a small company, we would like to avoid a refusal to file notice. Can you confirm that the Division will accept for filing our NDA based on the results of the ARG-911 trial which we discussed on May 21, 1997? Dr. Talarico's statement on classification of the NDA as standard or priority being determined after receipt of the NDA appears to support our objective, but did not directly answer our original question.

The second question deals with our historical control population in the ARG-911 study. As you pointed out at the May 21st meeting, our historical control mortality rate is lower than that for other published studies in HIT/HITTS, and per your wishes, we plan to place this issue in perspective in our review and summation of the trial data. In doing so, we were prompted to ask if the Division (or the Agency) has any specific criteria and standards for the collection of historical control cases, dealing with issues such as number of centers, number of cases per center, etc.? Our overriding concern has been to insure that the historical control population adequately reflects the natural course of the HIT/HITTS syndrome in medical practice, and that any potential differences between the patient characteristics in the historical controls and the prospectively treated patients can be properly adjusted for in the final analysis and report.

Realizing that you have not seen the complete study results, based on the data submitted and discussed at the May 21 meeting and assuming the final analysis continues to support the statistical outcomes and robustness of the data, and assuming adequate preclinical and in vitro studies, would you agree that study ARG-911 could support the claim of use as "anticoagulant therapy in patients with heparin-induced thrombocytopenia".

We look forward to your response. We are available today for a telephone discussion of these items at your convenience.

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Memo to: Ms Julieann DuBeau
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug Products (HFD-180)
FDA CDER
FAX No. 301-443-9285

From: Gary Knappenberger
Senior Director, Clinical Development and Regulatory Affairs
Texas Biotechnology Corporation

Subject: NOVASTAN[®] (argatroban)
Teleconference participants

Below is our list of expected participants in the teleconference scheduled for Friday, July 18, at 1:15 pm EDT with Dr Talarico, Dr. Sizer, Dr. Markovic, Dr. Sankoh, and yourself.

Gary Knappenberger
Senior Director, Clinical Development and Regulatory Affairs
Texas Biotechnology Corp.

Richard P. Schwarz, Jr., Ph.D.
Vice President, Clinical Development and Regulatory Affairs
Texas Biotechnology Corp

Catherine K. Clark
Director, North American Regulatory Affairs
SmithKline Beecham Pharmaceuticals

Deanne D. Garver, Ph.D.
Project Director, Research and Development
SmithKline Beecham Pharmaceuticals

Jeffrey R. Granett, M.D., F.A.C.C.
Group Director, Cardiopulmonary Therapeutic Unit,
Clinical Research, Development, and Medical Affairs
SmithKline Beecham Pharmaceuticals

We will contact you at 301-443-0487 at 1:15 pm Friday.

Printed by Julieann DuBeau
Electronic Mail Message

Sensitivity: COMPANY CONFIDENTIAL

Date: 30-Sep-1997 06:58am
From: Brenda Uratani

Dept: | _____
Tel No: | _____

TO: Julieann DuBeau (DUBEAUJ)
CC: Brenda Uratani (URATANIB)
Subject: Novastan filing meeting

Hi Julieann,

I have read through the Novastan submission and determine that it is fileable with respect to microbiology. I won't be attending the filing meeting this Thursday. Please keep me informed of the outcome of the meeting. Thanks.

Brenda

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL