CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-883

APPROVAL LETTER

NDA 20-883

JUN 3 0 2000

Texas Biotechnology Corporation
Attention: Mr. Daniel J. Thompson
7000 Fannin, Suite 1920
Houston, Texas 77030

Dear Mr. Thompson:

Please refer to your new drug application (NDA) dated August 11, 1997, received August 15, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ACOVA™ (argatroban) Injection.

We acknowledge receipt of your submissions dated February 24, March 2, April 20 and 26, May 3, and June 1, 19, and 20, 2000. Your submission of May 3, 2000, constituted a complete response to our February 18, 2000, action letter.

This new drug application provides for the use of ACOVA™ (argatroban) Injection as an anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert) and submitted draft labeling (immediate container and carton labels submitted April 20, 2000) incorporating the deletion of any reference to JP, Japanese Pharmacopeia, and USP from the immediate container and carton labels. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternately, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved NDA 20-883." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your Phase 4 commitments specified in your submission dated June 20, 2000. These commitments, along with any completion dates agreed upon, are listed below.

1. To conduct pharmacokinetic and safety studies in pediatric subjects to allow for appropriate dosing instructions in this population.

2. To conduct appropriate *in vitro* cardiac electrophysiologic studies and studies in cardiac compromised animal models. Specifically,

   (a) the following *in vitro* cardiac electrophysiologic studies:

      (i) action potential study in rabbit purkinje fibers,
      (ii) voltage clamp studies in isolated ventricular myocytes for determining effects on potassium, sodium, and calcium currents, and
      (iii) effects of HERG Channels in transfected human cells *in vitro*.

   (b) the following studies in cardiac compromised animal models:

      (i) anesthetized dog model to study regional myocardial blood flow and contractile function distal to a severe flow-limiting stenosis of the left circumflex coronary artery, and
      (ii) induced heart failure model in dogs.

Protocols, data, and final reports should be submitted to your IND for this product and a copy of the cover letter sent to this NDA. If an IND is not required to meet your Phase 4 commitments, please submit protocols, data and final reports to this NDA as correspondence. In addition, under 21 CFR 314.81(b)(2)(vii), we request that you include a status summary of each commitment in your annual report to this NDA. The status summary should include the number of patients entered in each study, expected completion and submission dates, and any changes in plans since the last annual report. For administrative purposes, all submissions, including labeling supplements, relating to these Phase 4 commitments must be clearly designated "Phase 4 Commitments."

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). We note that you have not fulfilled the requirements of 21 CFR 314.55 (or 601.27). We are deferring submission of your pediatric studies until December 2, 2002. However, in the interim, please submit your pediatric drug development plans within 120 days from the date of this letter unless you believe a waiver is appropriate. Within approximately 120 days of receipt of your pediatric drug development plan, we will review your plan and notify you of its adequacy.

If you believe that this drug qualifies for a waiver of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within

120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

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

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Gastrointestinal and Coagulation Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

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

Sincerely,

/S/ 6/30/00 for

Florence Houn, M.D., M.P.H., F.A.C.P.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-883

APPROVABLE LETTER

NDA 20-883

FEB 18 2000

Texas Biotechnology Corporation
Attention: Mr. Daniel J. Thompson
7000 Fannin, Suite 1920
Houston, TX 77030

Dear Mr. Thompson:

Please refer to your new drug application (NDA) dated August 11, 1997, received August 15, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Novastan® (argatroban) Injection.

We acknowledge receipt of your submissions dated April 9 and 14, May 11, June 22, July 8 and 20, August 11, December 11 and 17, 1998, March 17, April 27, May 17, June 2, 4, 17, and 29, July 2 and 6, August 13, December 17 and 28, 1999. Your submission of August 13, 1999, constituted a complete response to our May 8, 1998, action letter.

This new drug application provides for the use of Novastan® (argatroban) Injection as an anticoagulant for prophylaxis or treatment of thrombosis in patients with heparin-induced thrombocytopenia.

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

1. Please commit to conducting Phase IV pediatric studies with Novastan® (argatroban) Injection to adequately address in the labeling the use of this drug product in the pediatric population. The Agency believes that these studies are warranted for the following reasons: (1) the pediatric population can develop heparin-induced thrombocytopenia, (2) the dosing recommendations in the pediatric population are likely to be different from adults, and (3) some pediatric patients who are intolerant of heparin have a need for alternative anticoagulation.

2. Please commit to conducting Phase IV *in vitro* cardiac electrophysiologic studies and studies for effects in cardiac compromised animal models. The Agency noted higher mortality due to cardiac events in the Novastan® treated patients who had pre-existing cardiac conditions compared to the new historical controls.

3. Please provide an acceptable trade name for your drug product. Alternatively, provide justification for maintaining the current name of "Novastan". As you have been informed, the trade name "Novastan" may be confused with other similar names, e.g., "Novantrone", "Lovastatin".

In addition, it will be necessary for you to submit draft labeling incorporating the requested revisions as identified in the enclosed marked-up draft labeling as well as the following revisions to the immediate container and carton labels (submitted March 17, 1999):

1. The concentration of the drug product written on the carton and immediate container labels is defined as "2.5 mL (100 mg/mL)" while in the package insert it is "250 mg/2.5 mL". Even though these two terms represent the same concentration, they may be confusing. Please select one terminology for the package insert, immediate container, and carton labeling. We recommend the following presentation: "250 mg/2.5mL (100 mg/mL)."

2. Revise the storage statement on the carton label to read as follows: "Store at 25°C (77°F) excursion permitted to 15-30°C (59-86°F)."

3. The word "argatroban" written on the immediate container and carton labels should be half the size of the word "Novastan."

4. Delete the word "concentrate" from the immediate container and carton labels.

5. The name of the drug product written on the carton and immediate container labels is "Novastan® (argatroban) Injection Concentrate" while in the package insert it is expressed in a variety of ways including "Novastan®, brand of argatroban injection concentrate", "Novastan® (argatroban) Injection Concentrate" and "Novastan®". Please select one name for the drug product for the package insert, immediate container, and carton labeling.

6. The statement of ingredients, "Each 2.5 ml ...", should be consistent on both the immediate container and carton labeling.

7. Replace the "CAUTION: Federal law prohibits dispensing without prescription, " statement with "Rx only". We recommend placing "Rx only" on the center of the immediate container label and the main panel of the carton label.

8. Move the statement "DILUTE PRIOR TO USE" on the front panel of the carton label to appear immediately beneath the strength. In addition, we recommend deleting the line that separates the top portion of the left, front, and right panels from the bottom portion.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.

2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.

3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.

5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.

6. English translations of any approved foreign labeling not previously submitted.

7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Gastrointestinal and Coagulation Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

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

Sincerely,

/S/ 2/18/00

Victor F. C. Raczkowski, M.D.
Deputy Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure (Marked-up Draft Labeling)

cc:
Archival NDA 20-883
HFD-180/Div. Files
HFD-180/J.DuBeau
HFD-180/Reviewers and Team Leaders
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-103/ADRA (with labeling)
HFD-104/Peds/V.Kao (with labeling)
HFD-40/DDMAC (with labeling)
HFI-20/Press Office (with labeling)
HFD-400/OPDRA (with labeling)
HFD-613/OGD (with labeling)
HFD-095/DDMS-IMT (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE
R/d Init: Talarico 2/16/00
R/d Init: Raczkowski 2/17/00 VFR 2/18/00
JD/February 16, 2000 (drafted)
JD/2/18/00/c:\mydocs\nda\20883002-action-ltr.doc

APPROVABLE (AE)