FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

MEMORANDUM

DATE: February 21, 2013

FROM: Kimberly Lindsey, MD, Medical Officer, Clinical Review Branch, Division of Hematology, OBRR

SUBJECT: STN 125248.370 Complete Response to Labeling Prior Approval Supplement for RECOTHROM mid cycle clinical review memo

Date of Submission: September 14, 2012

Action Due Date: March 15, 2013

SPONSOR: Zymogenetics/ Bristol-Myers Squibb

TO: File for STN 125248.370

THROUGH: Nisha Jain, MD, Chief, Clinical Review Branch

CC: Cherie Ward-Peralta, Regulatory Project Manager, RPM Branch, Division of Blood Applications, OBRR

Recommendation:
Approval is recommended for the attached prescribing information for RECOTHROM. This recommendation also includes a pediatric indication for use of RECOTHROM in children ages 1 month to 16 years.

Contents of Submission:
Response to complete response letter issued on May 18, 2012. Specifically, the submission contains:

- Revised package insert for RECOTHROM
- Pooled analysis dataset tables to support revised adverse reactions text.

Background:

November 16, 2011: Original Prior Approval Labeling supplement (PAS) submission

The purpose of the original prior approval labeling supplement (STN 125248.370), submitted November 16, 2011, was to add updated safety information from two Phase 4 postmarketing requirement studies to the RECOTHROM package insert.

Study (499H01) was a pediatric postmarketing required study. The final study report for this trial was submitted to FDA on July 12, 2010. The second study (499G02) was a required postmarketing safety study to evaluate immunogenicity and safety of repeat exposure to RECOTHROM. The final clinical study report for this trial was submitted to FDA on December 15, 2010.

A complete response letter was issued to the sponsor on May 18, 2012. The complete response letter outlined several labeling deficiencies which precluded approval. Importantly, the package insert contained highly promotional material and did not reflect a fair balance of the available data and minimized the potential risks of product exposure. The entire complete response letter is attached to this memo as **Appendix 1**.

A follow up teleconference between FDA and the sponsor was held on July 31, 2012. During that teleconference the sponsor requested clarification of adverse events to be included in section 6, Adverse Reactions, of the package insert. During that teleconference, FDA requested the dataset tables used to support the new proposed text for adverse reactions, "6% embolic and thrombotic events were reported for RECOTHROM treated patients across clinical trials."

April 25, 2012: Pediatric Review Committee Presentation

RECOTHROM pediatric assessment data were presented to the FDA Pediatric Review Committee (PeRC) on April 25, 2012. A total of 30 pediatric patients aged 0 to 16 years (n=10 aged 1 month to 2 years; n=12, aged 2 to 12 years; and n=8 aged 12 to 16 years) were treated with RECOTHROM during Phase 2 and Phase 4 open-label, single-group studies in which RECOTHROM was applied by spray applicator to burn wound excision sites prior to autologous skin grafting. The sponsor chose to evaluate immunogenicity in burn surgery because patients are often subject to repeat surgical excisions requiring adjuncts to hemostasis, such as topical thrombin, to control bleeding.

The PeRC agreed with the Division's assessment that RECOTHROM can be labeled for use in 1 month -16 year old patients for the stated indications.

The following are highlights of the discussion regarding the pediatric assessment.

- The Division was advised to clarify with the sponsor whether any newborns (ages 0-28 days) were enrolled in to studies. In response to the request, the sponsor noted in amendment STN 125248.370/1 that no neonates were treated with RECOTHROM.
- The Division was advised to determine if a waiver in the neonatal pediatric population is justified or whether the postmarketing requirement (PMR) will be

continued to collect further data in the youngest patients. If additional data are needed in neonates, the Division has the option to not release the sponsor from the Pediatric Research Equity Act (PREA) PMR and request additional studies or to introduce a pediatric registry.

Regarding the package insert portions pertaining to the pediatric population:

- The PeRC recommended that the Division:
  - Modify the language in the pediatric usage section of the package insert (section 8.4) to state that safety cannot be extrapolated.
  - Consolidate adverse reaction data into the special populations section, pediatric usage (section 8.4) of the label.
  - Determine if a waiver in the neonatal pediatric population is justified or whether the PMR will be continued to collect further data in the youngest patients. If additional data are needed in neonates, the Division has the option to not release the sponsor from the PREA PMR and request additional studies or to introduce a pediatric registry.

Final actions:

The Division elected to accept the pediatric PMR study and no additional pediatric studies were requested. The pediatric labeling was revised to state:

"A total of 30 pediatric patients, ages 0 to 16 years (one month to 2 years, n=10; 2 to 12 years, n=12; 12 to 16 years, n=8), were treated in clinical trials with RECOTHROM using a spray applicator to burn wound excision sites prior to autologous skin grafting. No patient experienced a thromboembolic adverse reaction. The safety of RECOTHROM in pediatric patients greater than or equal to one month of age is supported by these data and by extrapolation of efficacy from adequate and well-controlled studies of RECOTHROM in adults. Safety and efficacy have not been established in neonates [see *Adverse Reactions (6)*]."

The Division extended the indication for RECOTHROM to include use in the pediatric population ages 1 month to 16 years.

Additionally, the dataset tables provided by the sponsor to support the statement: "The most common adverse reaction (incidence 6%) was thromboembolic events" is accurate.

The approvable package insert is appended to this memorandum. The clinical review memorandum for the required post marketing required pediatric study is also attached to this memorandum.

Attachment 1: May 18, 2012 Complete Response Letter

Our STN: BL 125248/370

ZymoGenetics, Inc.
Attention: Mr. Dale V. Goodloe
1201 Eastlake Ave East
Seattle, WA 98102

Dear Mr. Goodloe:

This letter is in regard to your supplement to your biologics license application (BLA) for Thrombin topical (Recombinant), to update the safety information from two Phase 4 studies to the RECOTHROM label, submitted under section 351 of the Public Health Service Act (42 U.S.C. 262).

We have completed our review of all the submissions you have made relating to this BLA supplement. After our complete review, we have concluded that we cannot grant final approval because of the deficiencies outlined below.

LABELING:

Note: Line numbers refer to the red-line strike out version of the package insert received on May 18, 2012 STN 125248\370\4 eCTD sequence number 0257). The corresponding line numbers on the clean copy of the package insert appear in parentheses.

1. Line 191 (188): Delete the reference to THROMBIN-JMI®, Thrombin, Topical [Bovine]. This information is presented as a footnote at the end of Table 1.

2. Lines 194-195 (191-192): Delete the following statement: "Categories of adverse reactions were identified for evaluation based on thrombin's mechanism of action or use with absorbable gelatin sponge, USP." The statement is misleading suggesting that only thrombin's mechanism of action or use with the gelatin sponge is a potential cause of adverse reactions.

3. Lines 208-212 (205-209) describe the phase 2 studies which included subjects undergoing a variety of surgical procedures (spinal surgery, hepatic resection, peripheral arterial bypass surgery, or arteriovenous graft formation for hemodialysis access. The inclusion of this information should mention the name of the placebo.

4. Lines 238-244 (235-241) describe an immunogenicity study. The information regarding the single patient who developed anti-CHO antibodies is missing from this study description. Please reinsert this information as it is presented in the current label.

5. Lines 245-246 (242-243) state: "Treatment with RECOTHROM resulted in a statistically significantly lower incidence of specific anti-product antibody development." This may be factually correct, but it implies that this is clinically significant. Please insert the following statement immediately after the sentence:

   "Because the study was not powered to detect a difference in clinical outcomes attributable to antibody formation, no conclusions can be drawn regarding the clinical significance of the difference in antibody formation based on the results of this study."

6. Under section 13.2 Animal Toxicology and/or Pharmacology, please refrain from using the word "tolerated" since it does not have a specific meaning. In your comments you provide information that specifies the clinical meaning of tolerated: i.e. "no effect on clinical signs, food consumption, body weights, serum chemistry, hematology, coagulation parameters, urinalysis, or organ gross pathology or histopathology after single or repetitive doses; only normal postsurgical findings were observed." An abbreviated description of these clinical findings, in lieu of the word "tolerated," is acceptable.

7. We reserve further comment on the proposed labeling until the supplement is otherwise acceptable. We may have comments when we see the proposed final labeling.

8. Should additional information relating to the safety and effectiveness of this drug product become available before our receipt of the final printed labeling, revision of that labeling, may be required.

We stopped the review clock with the issuance of this letter. We will reset and start the review clock when we receive your complete response.

Within 10 days after the date of this letter, you should take one of the following actions: (1) amend the supplement; (2) notify us of your intent to file an amendment; or (3) withdraw the supplement.

As per our teleconference with Agency representatives on May 17, 2012, you have committed to submitting a response to this letter within one month of the receipt of this complete response letter.

You may request a meeting or teleconference with us to discuss the steps necessary for approval. For PDUFA products please submit your meeting request as described in our "Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants," dated May 2009.

This document is available on the internet at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf or may be requested from the Office of Communication, Outreach, and Development, at (301) 827-1800. For non-PDUFA products, please contact the regulatory project manager. For details, please also follow the instructions described in CBER's SOPP 8101.1: Scheduling and Conduct of Regulatory Review Meetings with Sponsors and Applicants. This document also is available on the internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/ucm079448.htm or may be requested from the Office of Communication, Outreach, and Development.

Please be advised that, as stated in 21 CFR 601.3(c), if we do not receive your complete response within one year of the date of this letter, we may consider your failure to resubmit to be a request to withdraw the supplement. Reasonable requests for an extension of time in which to resubmit will be granted. However, failure to resubmit the supplement within the extended time period may also be considered a request for withdrawal of the supplement.

If you have any questions regarding the above, please contact the Regulatory Project Manager, Cherie Ward-Peralta, at (301) 827-9170.

Sincerely yours,

Basil Golding, M.D.
Director
Division of Hematology
Office of Blood Research and Review
Center for Biologics
Evaluation and Research