MEMORANDUM

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Center for Biologics Evaluation and Research (CBER)

Re: STN 125248

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Product: RECOTHROM® [Thrombin, topical (recombinant)]

Subject: Pediatric Safety and Utilization Review for the Pediatric Advisory Committee (PAC) Meeting

Sponsor: The Medicines Company (previously Zymogenetics, Inc.)

Approval Date: 01/17/2008 approval for use as an adjunct to hemostasis when control of bleeding by conventional surgical techniques (including suture, ligature, and cautery) is ineffective, insufficient, or impractical.

03/15/2013 approval to revise the product label to include safety information from two Phase 4 Post-marketing requirement studies, and a pediatric indication for use of RECOTHROM® in children greater than or equal to one month of age.
1. Introduction
RECOTHROM® [Thrombin topical (recombinant)] is a recombinant thrombin used as an adjunct to hemostasis. It is supplied as a lyophilized powder, which is then reconstituted to liquid. It can be used with an absorbable gelatin sponge, or with the Zymogenetics Spray Applicator kit. Thrombin products, including older bovine-derived products and the plasma-derived product, Evithrom® [Thrombin, topical (human)], have been in use for many years. RECOTHROM® is the first clotting solution made using recombinant DNA technology. RECOTHROM® is made from Chinese Hamster Ovary cells, which have been genetically modified to produce human thrombin.

RECOTHROM® was approved for use as an adjunct to hemostasis on 01/17/2008. The indication was revised to specify use in pediatric populations greater than or equal to 1 month of age on 03/15/2013. The revised indication specifying use in pediatric populations is the trigger for this pediatric utilization and safety review and presentation to the Pediatric Advisory Committee (PAC).

2. Objectives
The objective of this memorandum is to provide a safety review for RECOTHROM® from March 15, 2013 to March 15, 2015, the 24-month time frame following approval of the revised indication for pediatric use. The purpose is to determine if there is any evidence of new safety concerns that might have emerged since the indication was revised to include pediatric populations.

An abbreviated presentation to the PAC is planned for this product because none of the criteria that would trigger a full oral presentation or justified abbreviated presentation to the PAC have been met. Specifically, there were no pediatric deaths reported during the review period. Additionally, there were no new safety signals identified, no label changes related to safety during the review period, and there are no post-marketing requirement studies or REMS planned or in place. Although the PAC presentation is abbreviated, the analysis of the safety data is comprehensive, and this memorandum documents FDA’s full evaluation, including review of adverse event reports in passive surveillance data, periodic safety update reports and post-market study results from the manufacturer, and a review of published literature.

3. Materials Reviewed
4.1 FDA Documents
Recothrom Approval letter, dated 01/17/2008
Recothrom Approval letter, dated 03/15/2013

4.2 Manufacturer’s Submissions

1 Thrombin JMI Thrombin, topical (bovine) was approved in 1995 under STN 102865

2 Fractionated Plasma Products>March 15, 2013 Approval Letter-RECOTHROM
4. Pediatric Label Changes since Licensure

At the time of initial FDA licensure, RECOTHROM® was approved as an aid to hemostasis whenever oozing blood and minor bleeding from capillaries and small venules is accessible and control of bleeding by standard surgical techniques (such as suture, ligature or cautery) is ineffective or impractical.

On March 15, 2013, FDA approved revisions to the product label to include pediatric populations greater than or equal to one month of age in the indication and addition of safety information, including pediatric safety, from two post-marketing studies: a pediatric study required under the Pediatric Research Equity Act (PREA) and a clinical study evaluating immunogenicity and safety of re-exposure to Recothrom. These studies are discussed further under Section 6.1, Postmarketing Studies.

5. Product Distribution Data

Data for estimating patient exposures to RECOTHROM® is supplied by the sponsor, The Medicines Company. An estimated 443,504 pediatric patients were exposed to RECOTHROM® between January 17, 2008 (date of original approval) and March 13, 2015. These data are based on shipment information that tracks RECOTHROM® from wholesalers to purchasing hospitals. RECOTHROM® is used in a hospital or medical facility only, and actual prescription or other usage data are not available. In order to estimate the number of pediatric patients exposed, the number of vials purchased by pediatric hospitals was determined from the data sources described below. The manufacturer reports that this estimate is likely a conservative estimate, as pediatric exposures occurring in hospitals treating both adult and pediatric patients could not be determined.

The Medicines Company abstracted data from two different commercially available pharmaceutical data sources (IMS and Symphony Health Solutions [formerly Wolters-Kluwer]) and internal sales reports in order to obtain hospital-level purchasing information for pediatric hospitals over the commercial life of the product. Based on distribution to pediatric hospitals, The Medicines Company estimated that 443,504 pediatric patients were exposed to RECOTHROM® between January 17, 2008 and March 13, 2015. This includes 30 pediatric

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3http://www.fda.gov/biologicsbloodvaccines/bloodbloodproducts/approvedproducts/licensedproductsblas/fractionatedplasmaproducts/ucm089451.htm
patients included in clinical trials prior to January, 2010. The estimated number of pediatric patients exposed to RECOTHROM® between March 1, 2013 and March 13, 2015 is 172,144. The estimated number of total patient exposures between January 2008 and December 2014 is 4,322,835, and the total patient exposures between January 2013 and December 2014 is 1,676,103.

6. Pharmacovigilance Plan
RECOTHROM® was initially approved in 2008. At the time of approval, the sponsor was required under PREA to conduct a study in pediatric subjects (study 499H01). The sponsor also committed to conduct a post-marketing study (499G02) to evaluate immunogenicity and safety of re-exposure to Recothrom®. Both post-marketing studies have been completed and are described below.

6.1 Post-Marketing Clinical Studies

<table>
<thead>
<tr>
<th>Study 499G02</th>
<th>Study 499H01</th>
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<tr>
<td><strong>Title</strong></td>
<td><strong>Title</strong></td>
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<tr>
<td><strong>Primary Purpose</strong></td>
<td><strong>Primary Purpose</strong></td>
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<tr>
<td>Evaluate immunogenicity and safety in subjects with prior exposure to rThrombin in completed Phase 3 study (study 499E01)</td>
<td>Evaluate the safety of rThrombin in surgery for burn wound excision and skin grafting in pediatric subjects</td>
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<tr>
<td><strong># subjects</strong></td>
<td><strong># subjects</strong></td>
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<tr>
<td>31 adult subjects, 30 completed study</td>
<td>30 pediatric patients, at least 3 in each age category (0-2, 3-6, 7-11, 12-17)</td>
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<tr>
<td><strong>Deaths</strong></td>
<td><strong>Deaths</strong></td>
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<tr>
<td>1 subject died on day 23 due to cardiopulmonary failure due to sepsis, deemed by investigators as not related to study drug</td>
<td>There were no pediatric deaths</td>
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<tr>
<td><strong>Adverse Events</strong></td>
<td><strong>Adverse Events</strong></td>
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<td>No subjects discontinued due to adverse events. Pain, constipation, and nausea were the most commonly reported adverse events. Most subjects (n=29/31; 93.5%) experienced at least 1 adverse event. All adverse events were considered by the investigators as unrelated to treatment with rThrombin.</td>
<td>1 subject experienced the treatment emergent serious adverse events of skin graft infection and skin graft failure. Both were considered by the investigator as not related to study treatment. Evaluation for immunogenicity showed that none of the subjects developed anti-recothrom antibodies.</td>
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The sponsor concluded that subjects with prior exposure to recombinant thrombin do not appear to be at high risk for developing anti-drug antibody after subsequent exposure.

In general, administration on rThrombin was well tolerated. The incidence and type of adverse events were as expected in a surgical population undergoing synchronous burn wound excision and skin grafting.

### 7. Adverse Event Review

A search of the FDA Adverse Event Reporting System (FAERS) was performed on 04/30/2015 to identify adverse events occurring between January 17, 2008 and March 15, 2015. FAERS is a spontaneous adverse event reporting system with inherent limitations including under reporting, delayed reporting and variable report accuracy. It is generally not possible to determine causality.

#### 7.1. Results

There were no pediatric adverse events reported since January 17, 2008. There were a total of 29 non-pediatric adverse events reported from January 17, 2008 through March 15, 2015. Of the 29 reports, there were 4 instances of duplicate reporting, resulting in 25 unique reports. Of the 25 reports, two reports received during the time interval after approval of the pediatric age indication March 15, 2013 through March 15, 2015. Neither of these adverse event reports were associated with a patient injury; both were reports of packaging complaints.

There were a total of 3 packaging complaints from January 2008 through March 2015. All reports were reviewed. None of the 3 reports were of the same complaint. One involved a bent spike on an adapter used for puncturing the vial, one noted that the product comes with an IV-compatible syringe which could lead to misadministration, and one reported incomplete markings on one package.

RECOTHROM® is licensed in the US and Canada, but only marketed in the US. As such, all of the cases are domestic. There were 5 reports of medication error, either in dosing or in route of administration. None of these reports resulted in patient injury.

Note that a single report may be associated with more than one adverse event term.

### Table 1) Adverse event reports for RECOTHROM in FAERS received between 17 Jan 2008 and 15 Mar 2015

<table>
<thead>
<tr>
<th>Age</th>
<th>Serious US</th>
<th>Serious Foreign</th>
<th>Death US</th>
<th>Death Foreign</th>
<th>Non-Serious US</th>
<th>Non-Serious Foreign</th>
<th>Total US</th>
<th>Total Foreign</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;16 yo</td>
<td>29</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>29</td>
<td>0</td>
</tr>
<tr>
<td>0-16 yo</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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### Table 2) Most Frequently Reported Adverse Event Terms in Adult reported AEs
### 7.2. Notable Cases
The most commonly reported adverse event was venous occlusion. These reports include a single report of venous occlusion occurring after use for treatment of a pseudoaneurysm (contraindicated use), and 5 cases occurring after inadvertent intravascular administration during cranietomy procedures that was described in a literature report (“Iatrogenic cerebral venous sinus occlusion with flowable topical hemostatic matrix”, published in the Journal of Neurosurgery). In these cases, RECOTHROM® was used during craniectomy and venous occlusion occurred due to inadvertent intravascular administration. None of these reports resulted in death, and none developed long term neurologic sequelae. The authors noted that the choice of when to use these products and modification in application techniques may minimize the risk of vascular occlusion. The RECOTHROM® product label directs users to “topically apply RECOTHROM solution directly or in conjunction with absorbable gelatin sponge onto the bleeding site. DO NOT INJECT.” The Contraindications section of the label states: “Do not inject into the circulatory system,” and the Warnings and Precautions section states: “RECOTHROM may cause thrombosis if it enters the circulatory system.”

### 7.3. Deaths
There were no death reports in the reporting interval of March 15, 2013 to March 15, 2015. There was one death reported since approval on January 17, 2008. This case involves an elderly male who underwent mediastinal biopsy in 2008. Thrombin was “laced” around a needle tract to aid in hemostasis. Immediately after the procedure, the patient developed confusion and seizure and subsequently died. CT scan showed left middle cerebral artery stroke and cerebellar stroke. As noted above, the label directs users to topically apply RECOTHROM® directly or via an absorbable sponge, and the Contraindications section of the label states that RECOTHROM® should not be injected into the circulatory system.

### 7.4. Pediatric Cases
There were no pediatric cases reported since approval on January 17, 2008.

### 7.5. Device Review
Query of the MAUDE database revealed no device related adverse events for RECOTHROM® or the spray applicator kit reported to MAUDE from January 17, 2008 through March 15, 2015.

### 8. Literature Review
PubMed Search for “Recothrom”, “Human Thrombin, Recombinant” performed March 18, 2015 retrieved 7 articles. The articles describe comparison of RECOTHROM® and Bovine Thrombin, immunogenicity and use for the off-label indication of pseudoaneurysm treatment. Review of the articles did not identify any new safety concerns related to RECOTHROM®.

1. **Cross-reactivity of various thrombin products with anti-rabbit antibodies to bovine, human, and recombinant thrombin.**

Anti-Recothrom antibodies can cross-react with Evithrom and JMI in a time dependent manner.

2. Results of a new human recombinant thrombin for treatment of arterial pseudoaneurysm.

Human recombinant thrombin (Recothrom) is a safer non-immunogenic option with similar success rates as other fibrin glue sealants.

3. Immunogenicity and safety of re-exposure to recombinant human thrombin in surgical hemostasis.

The immunogenicity and safety results of this Phase 4 rThrombin trial suggest that patients with known previous exposure may be safely re-exposed to topical rThrombin.

4. Cross-reactivity of rabbit anti-bovine thrombin IgGs with human alpha-thrombin and a recombinant version of human thrombin (Recothrom).

Patients who were previously exposed to bovine thrombin may also develop antibodies which can cross-react with human recombinant thrombin.

5. (b) (4)


Inadvertent intravascular administration of flowable topical hemostatic matrix is a rare complication of cranial surgery that occurs most commonly during procedures around the transverse and/or sigmoid sinuses. Modification in the choice of when to use a flowable topical hemostatic matrix, and the method of application, may prevent accidental venous sinus administration.

7. Ultrasound-guided percutaneous thrombin injection of iatrogenic upper extremity pseudoaneurysms.
Ultrasound-guided percutaneous thrombin injection appears safe and effective for the treatment of iatrogenic brachial and radial artery pseudoaneurysms

9. Conclusion
This comprehensive post marketing safety review of pediatric post-market data from the manufacturer, passive surveillance adverse event reports, and the published literature does not indicate any new safety concerns for Recothrom®. There were no death reports and no pediatric reports during the reporting interval of March 15, 2013 through March 15, 2015, and no pediatric reports since approval January 17, 2008. Recothrom® has few adverse events reported given the volume of distribution. The single death report, as well as several of the thromboembolic adverse event reports, followed use of the product for unlabeled indications or in manners inconsistent with the labeled instructions for use. The adverse event of thrombosis is clearly labeled, in multiple locations in the package insert. The label contains adequate instructions and warnings for safe use.

10. Recommendations
FDA recommends continued monitoring for new and existing safety signals. No further regulatory action is indicated at this time.