RETHINK YOUR THROMBIN

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INDICATION

RECOTHROM Thrombin, topical (Recombinant) is indicated 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.

IMPORTANT SAFETY INFORMATION

Contraindications

- **Topical use only – DO NOT INJECT directly into the circulatory system**
- **Do not use for the treatment of massive or brisk arterial bleeding** or in patients with known hypersensitivity to RECOTHROM, any components of RECOTHROM or hamster proteins

Warnings and Precautions

- **Potential risk of thrombosis if absorbed systemically**
- In patients with known hypersensitivity to snake proteins, there may be a potential for allergic reaction

Adverse Reactions

- The serious adverse event that occurred in ≥1% (n=6/583) of patients exposed to RECOTHROM in completed clinical trials was atrial fibrillation. The most common adverse events reported in these trials (N=583) were incision site pain (51%), procedural pain (30%), and nausea (28%). Adverse events reported in these trials were consistent with those commonly observed in surgical patients

RECOTHROM®
THROMBIN, TOPICAL
(RECOMBINANT)

Please see Brief Summary of full Prescribing Information on next page.

ZymoGenetics™
A Bristol-Myers Squibb Company

RECOTHROM®
THROMBIN, TOPICAL
(RECOMBINANT)

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

RECOTHROM® Thrombin, topical (Recombinant)

Rx Only
The following is a brief summary of the full prescribing information for RECOTHROM Thrombin, topical (Recombinant).

CONTRAINDICATIONS
- **Do not inject directly into the circulatory system.**
- **Do not use for the treatment of massive or brisk arterial bleeding.**
- Do not administer to patients with known hypersensitivity to RECOTHROM, any components of RECOTHROM, or hamster proteins.

WARNINGS AND PRECAUTIONS
- **Potential risk of thrombosis if absorbed systemically.**
- In patients with known hypersensitivity to snake proteins, there may be a potential for allergic reaction.

ADVERSE REACTIONS
The serious adverse event that occurred in ≥ 1% (n=6/583) of patients exposed to RECOTHROM in completed clinical trials was atrial fibrillation. The most common adverse events in patients exposed to RECOTHROM in clinical trials (N=583) were incision site pain (51%), procedural pain (30%), and nausea (28%).

Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug product cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Clinical trials have been performed with RECOTHROM applied with absorbable gelatin sponge (Phase 2, Phase 3, and Phase 3b studies) and applied with a spray applicator (Phase 2 study). Adverse events reported in clinical trials were consistent with those commonly observed in surgical patients.

• Clinical Trials of RECOTHROM Used in Conjunction with Gelatin Sponge
Among the 411 patients treated with study drug in the randomized, double-blind, Phase 3 study that compared RECOTHROM to bovine thrombin, both applied with gelatin sponge, in patients undergoing spinal surgery, hepatic resection, peripheral arterial bypass surgery, or arteriovenous graft formation for hemodialysis access, all but 2 patients (1 patient/treatment group) reported adverse events. Most events were moderate in severity and had a similar incidence in the RECOTHROM and bovine thrombin treatment groups. The most common adverse events were incision site pain (63% for both treatment groups), procedural pain (RECOTHROM 29%; bovine thrombin 34%), and nausea (RECOTHROM 28%; bovine thrombin 35%). Serious adverse events were reported by 18% of patients treated with RECOTHROM and 22% with bovine thrombin.

Adverse events of interest were pre-specified, based on the thrombin mechanism of action, use of absorbable gelatin sponge, USP, historical reporting in association with cross-reacting antibodies to bovine thrombin product, and results from Phase 2 clinical trials of RECOTHROM applied with absorbable gelatin sponge. The incidences of these pre-specified adverse events were similar between treatment groups (see Table 1).

Table 1. Events of Interest in the RECOTHROM Phase 3 Study

AE Category*	RECOTHROM (N=205) n (%)	Thrombin-JMI† (N=206) n (%)
Patients with any event category	124 (60%)	136 (66%)
Bleeding	27 (13%)	24 (12%)
Cardiac	41 (20%)	38 (18%)
Hypersensitivity	30 (15%)	37 (18%)
Nausea + vomiting	68 (33%)	83 (40%)
Other infection	26 (13%)	31 (15%)
Post-operative wound infection	19 (9%)	22 (11%)
Thromboembolic	12 (6%)	10 (5%)

*Adverse events were included in event categories based on a blinded review of the investigator verbatim and coded terms.
†THROMBIN-JMI® Thrombin, Topical (Bovine).

In an open-label, single-group Phase 3b study, 209 patients with documented or highly likely prior exposure to bovine thrombin within the previous 3 years were treated with RECOTHROM when undergoing surgeries (spinal or peripheral arterial bypass or arteriovenous graft formation for hemodialysis access). The most common adverse events were incision site pain (45%), procedural pain (39%), and nausea (27%). Similar to the Phase 3 study, serious adverse events were reported by 22% of patients treated with RECOTHROM.

• Clinical Trials of RECOTHROM Applied with Spray Applicator
In an open-label, single-group, Phase 2 study in burn patients, 72 patients were treated with RECOTHROM applied with a spray applicator at the burn wound excision site prior to autologous skin grafting. This study included both adults (≥ 17 years of age, n=68) and pediatric patients ≤ 16 years of age (n=4). The most common adverse events in the adult and pediatric age groups included procedural pain (35%), pruritis (25%), and constipation (19%).

• Immunogenicity
The potential development of antibodies to RECOTHROM has been evaluated in multiple clinical trials. These pre-specified evaluations were performed in order to characterize the immunogenicity of RECOTHROM and the neutralizing potential of any detected antibodies. In completed clinical studies 5 of 552 (0.9%) patients exposed to RECOTHROM with both baseline and post-treatment antibody specimens available developed specific anti-RECOTHROM product antibodies. None of these antibodies were found to neutralize native human thrombin.

In the randomized, double-blind, Phase 3 study that compared RECOTHROM to bovine thrombin, both applied with gelatin sponge, in patients undergoing spinal surgery, hepatic resection, peripheral arterial bypass surgery, or arteriovenous graft formation for hemodialysis access, the development of specific anti-product antibodies was evaluated in both treatment groups. Blood samples were collected at baseline and at day 29 for 97% of the patients in both treatment groups. For patients randomized to RECOTHROM, the samples were analyzed by ELISA for antibodies to RECOTHROM, Chinese hamster ovary (CHO) host cell protein, and pro-thrombin activator (used in the conversion of single chain precursor to active RECOTHROM). For patients randomized to bovine thrombin, the samples were analyzed by ELISA for antibodies to bovine thrombin product.

At baseline 1.5% of patients (n=3/198) in the RECOTHROM group had positive anti-product antibody titers compared with 5% of patients in the bovine thrombin group (n=10/200). Of the patients who had detectable anti-product antibodies at baseline, 0 of 3 in the RECOTHROM group and 8 of 10 in the bovine thrombin group exhibited ≥ 1.0 titer unit (≥ 10-fold) increases in antibody levels after study treatment.

Treatment with RECOTHROM applied with absorbable gelatin sponge resulted in a statistically significantly lower incidence of specific anti-product antibody development. Three of 198 (1.5%; 95% CI, 0 to 4%) of the patients in the RECOTHROM arm developed specific anti-thrombin product antibodies (1 patient also developed anti-CHO host cell protein antibodies). No patients developed antibodies to pro-thrombin activator. Forty-three of 200 patients (22%; 95% CI, 16 to 28%) in the bovine thrombin arm developed specific antibodies to bovine thrombin product. None of the antibodies in the RECOTHROM group neutralized native human thrombin. Antibodies against bovine thrombin product were not tested for neutralization of native human thrombin. 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.

In the open-label, single group, Phase 3b study in patients with a high likelihood of prior bovine thrombin exposure undergoing spinal, peripheral arterial bypass surgery, or arteriovenous graft formation for hemodialysis access, 15.6% of patients (n=32/205) had anti-bovine thrombin product antibodies at baseline prior to treatment with RECOTHROM. Following treatment, none of the 200 evaluable patients (patients for whom specimens were available for antibody testing at baseline and post-RECOTHROM treatment) developed antibodies to RECOTHROM.

In the randomized, double-blind, controlled Phase 2 studies of RECOTHROM compared to placebo (RECOTHROM excipients reconstituted with 0.9% sodium chloride, USP) applied in conjunction with absorbable gelatin sponge, which were performed across a range of surgical settings (spinal surgery, hepatic resection, peripheral arterial bypass surgery, or arteriovenous graft formation for hemodialysis access), the incidence of antibody development to RECOTHROM was 1.2% in the RECOTHROM group (n=1/83) compared to 2.4% (n=1/41) in the placebo group. In the open-label, single group Phase 2 study of RECOTHROM applied with the spray applicator to excised burn wounds, 1 patient developed antibodies following treatment (1.6%, n=1/62).

The detection of antibody formation is highly dependent upon the sensitivity and specificity of the assay. The absolute immunogenicity rates reported here are difficult to compare with results from studies of other products due to differences in assay methodology, patient populations, and other underlying factors.

To report SUSPECTED ADVERSE REACTIONS, contact ZymoGenetics, Inc. at 1-888-784-7662, or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS
Drug interactions have not been formally studied.

USE IN SPECIFIC POPULATIONS
• Pregnancy
Pregnancy Category C. Animal reproduction studies have not been conducted with RECOTHROM. It is also not known whether RECOTHROM can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. RECOTHROM should be given to a pregnant woman only if clearly needed.

• Pediatric Use
Of the 72 patients undergoing burn wound excision and grafting treated with RECOTHROM applied with the spray applicator in the open-label, single group, Phase 2 study, 4 were pediatric patients. All were age 12 to 16 years. The safety and effectiveness of RECOTHROM in all pediatric age groups have not been fully established.

• Geriatric Use
Of the total number of patients in Phase 2 and Phase 3 clinical studies of RECOTHROM with absorbable gelatin sponge, 38% were 65 years old and over, while 16% were 75 years old and over.

No substantive differences in safety or effectiveness were observed between these patients and younger patients, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

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