These highlights do not include all the information needed to use EIVITHROM safely and effectively. See full prescribing information.

EIVITHROM® Thrombin, Topical (Human) For Topical Use Only Initial U.S. approval: 2007

**INDICATIONS AND USAGE**

• As an aid to hemostasis whenever oozing blood and minor bleeding from capillaries and small vessels is accessible and control of bleeding cannot be achieved by standard surgical techniques, such as pressure or impalpable (1).

• May be used in conjunction with an Absorbable Gelatin Sponge, USP (1).

**DOSAGE AND ADMINISTRATION**

- For topical use only. DO NOT INJECT (2.2).
- The amount required depends upon the area of tissue to be treated and the method of application. In clinical studies, volumes up to 1 ml were used in conjunction with Absorbable Gelatin Sponge, USP (2.2).
- Thaw prior to use (2.1). The time between thawing and application is critical (2.2).
- Vials are for single use only. Discard unused contents (2.2).

**DOSE FORMS AND STRENGTHS**

- Vials of 2 ml, 5 ml or 20 ml frozen solution containing 800-1200 IU/ml of Thrombin, Topical (3).

**CONTRAINDICATIONS**

• Do not inject directly into the circulatory system (4).
• Do not use in individuals known to have anaphylactic or severe systemic reaction to human blood products (4).
• Do not use for the treatment of severe or brisk arterial bleeding (4).
• Do not use in patients who have had reactions to human blood products (4).

**FULL PRESCRIBING INFORMATION**

1 INDICATIONS AND USAGE

- EIVITHROM® (human recombinant thrombin) in a vial is indicated for an aid to hemostasis whenever oozing blood and minor bleeding from capillaries and small vessels is accessible and control of bleeding cannot be achieved by standard surgical techniques, such as pressure or impalpable.

2 DOSAGE AND ADMINISTRATION

2.1 Thawing prior to application

Thaw EIVITHROM in one of the following ways:

• 2°C to 8°C (refrigerated): Vials should thaw within 1 day.
• 20°C to 25°C (room temperature): Vials thaw within 1 hour.

2.2 Application techniques

- For topical use only. DO NOT INJECT.

- Vials are for single use only. Discard unused contents.

- Do not inject directly into the circulatory system. Do not use in individuals known to have anaphylactic or severe systemic reactions to human blood products.

- Do not use for the treatment of severe or brisk arterial bleeding.

3 DOSAGE FORMS AND STRENGTHS

EIVITHROM is supplied as a frozen solution in the following packages:

- Vials of 2 ml, 5 ml or 20 ml. Each vial contains 800-1200 IU/ml of Thrombin, Topical (Human).

4 CONTRAINDICATIONS

- Do not use in patients who have had reactions to human blood products (4).

5 WARNINGS AND PRECAUTIONS

5.1 Potential risk of transmitting infectious agent

- May carry a risk of transmitting infectious agents such as viruses and, theoretically, the Creutzfeldt-Jakob disease (CJD) agent, despite manufacturing steps designed to reduce the risk of viral transmission (11).

5.2 Potential risk of thrombosis if absorbed systemically (8.2, 11).

6 ADVERSE REACTIONS

6.1 Clinical trials experience

- Drug interations

**FULL PRESCRIBING INFORMATION**

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

- USE IN SPECIFIC POPULATIONS

- Geriatrics: No differences in safety or effectiveness were observed between the elderly and younger patients. Greater susceptibility of older patients to adverse reactions cannot be ruled out (8.5).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 9/2007

**ADVERSE REACTIONS**

- Anaphylactic reactions may occur (9).
- Adverse reactions were reported in the clinical trial with similar frequency in the two study groups (EIVITHROM or bovine thrombin group). The most common adverse event reported was procedural complications and pruritus (8). None of the adverse events reported was considered causally related to EIVITHROM administration.

- Immunogenicity was evaluated by testing for the development of antibodies to human thrombin, human Factor Va/Va, bovine thrombin and bovine Factor V/Va. None of the patients treated with EIVITHROM developed antibodies to human thrombin or to human Factor V/Va.

To report SUSPECTED ADVERSE REACTIONS, contact ETHICON Customer Support Center at (877) 384-4265 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

**CAUTIONS TO THE USE**

- Do not inject directly into the circulatory system.

- The physician or other healthcare provider to EIVITHROM Customer Support Center at (877) 384-4265. The physician should discuss the risks and benefits of this product with the patient.

- Potential risk of thrombosis if absorbed systemically (9).

**ADVERSE REACTIONS**

- Adverse reactions were reported in the clinical trial with similar frequency in the two study groups (EIVITHROM or bovine thrombin group). The most common adverse event reported was procedural complications and pruritus (8). None of the adverse events reported was considered causally related to EIVITHROM administration.

- Immunogenicity was evaluated by testing for the development of antibodies to human thrombin, human Factor Va/Va, bovine thrombin and bovine Factor V/Va. None of the patients treated with EIVITHROM developed antibodies to human thrombin or to human Factor V/Va.

To report SUSPECTED ADVERSE REACTIONS, contact ETHICON Customer Support Center at (877) 384-4265 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

**USE IN SPECIFIC POPULATIONS**

- Geriatrics: No differences in safety or effectiveness were observed between the elderly and younger patients. Greater susceptibility of older patients to adverse reactions cannot be ruled out (8.5).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 9/2007

**ADVERSE REACTIONS**

- Anaphylactic reactions may occur (9).
- Adverse reactions were reported in the clinical trial with similar frequency in the two study groups (EIVITHROM or bovine thrombin group). The most common adverse event reported was procedural complications and pruritus (8). None of the adverse events reported was considered causally related to EIVITHROM administration.

- Immunogenicity was evaluated by testing for the development of antibodies to human thrombin, human Factor Va/Va, bovine thrombin and bovine Factor V/Va. None of the patients treated with EIVITHROM developed antibodies to human thrombin or to human Factor V/Va.

To report SUSPECTED ADVERSE REACTIONS, contact ETHICON Customer Support Center at (877) 384-4265 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

**USE IN SPECIFIC POPULATIONS**

- Geriatrics: No differences in safety or effectiveness were observed between the elderly and younger patients. Greater susceptibility of older patients to adverse reactions cannot be ruled out (8.5).

See 17 for PATIENT COUNSELING INFORMATION

Revised: 9/2007

**ADVERSE REACTIONS**

- Anaphylactic reactions may occur (9).
- Adverse reactions were reported in the clinical trial with similar frequency in the two study groups (EIVITHROM or bovine thrombin group). The most common adverse event reported was procedural complications and pruritus (8). None of the adverse events reported was considered causally related to EIVITHROM administration.

- Immunogenicity was evaluated by testing for the development of antibodies to human thrombin, human Factor Va/Va, bovine thrombin and bovine Factor V/Va. None of the patients treated with EIVITHROM developed antibodies to human thrombin or to human Factor V/Va.

To report SUSPECTED ADVERSE REACTIONS, contact ETHICON Customer Support Center at (877) 384-4265 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.
Subjected undergoing elective cardiac, neurologic, spinal (minimal) or general surgical procedures were randomized (stratified by surgical specialty) when there was oozing or bleeding of mild intensity that could not be controlled by other surgical techniques and the surgeon determined that a topical hemostatic agent was necessary. Both bovine thrombin and EVITHROM were applied to SURGIFONT® Absorbable Gelfoam, SPUS.

Treatments with EVITHROM was as successful as treatment with bovine thrombin in achieving the primary efficacy endpoint: hemostasis within 10 minutes of product application and secondary efficacy endpoints: hemostasis within 6 and 3 minutes of product application.

14.4 The dose

EVITHROM was compared with bovine thrombin in a phase III, prospective, randomized, controlled, double-blind study of 305 subjects at 22 centers in the US.

Table 1: Reducing factors of S/D treatment and nanofiltration for a series of viruses

<table>
<thead>
<tr>
<th>Virus Type</th>
<th>Reduction Factor (log10)</th>
<th>Reduction Factor (log10)</th>
<th>Reduction Factor (log10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAV (10^7 c.c.)</td>
<td>6.82</td>
<td>5.31</td>
<td>4.74</td>
</tr>
<tr>
<td>HIV-1 (10^6 c.c.)</td>
<td>9.72</td>
<td>6.37</td>
<td>6.95</td>
</tr>
<tr>
<td>HIV-2 (10^6 c.c.)</td>
<td>9.72</td>
<td>6.37</td>
<td>6.95</td>
</tr>
</tbody>
</table>

14.2 Clinical Pharmacology

EVITHROM requires no intermediate physiological agent because it clots the fibrinogen of the blood directly. Failure to clot blood occurs in the rare case where the primary clotting defect is the absence of fibrinogen itself. The speed with which thrombin clots the blood is dependent upon the concentration of both thrombin and fibrinogen.

13.4 Preclinical Toxicology

In vivo toxicology studies performed in rats with the combination of TbTh and TnBP in the 100 c.c./kg dose group indicated no evidence of toxicity, as measured by body weight and food consumption. All animals in the combination group survived the entire study period and no adverse effects were observed. The combination of TbTh and TnBP in the 500 c.c./kg dose group indicated no evidence of toxicity, as measured by body weight and food consumption. All animals in the combination group survived the entire study period and no adverse effects were observed.

13.5 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been performed to evaluate the carcinogenic potential of EVITHROM due to the human origin of thrombin. Therefore, on fertility has not been evaluated.

Studie performed in bacteria to determine mutagenicity of human thrombin alone, TbTh alone or TbTh alone were negative at all concentrations tested. All concentrations of the combination of TbTh and TnBP also tested negative in bacteria, as measured by the reverse mutation test with S. typhimurium.

14.2 The dose

EVITHROM was compared with bovine thrombin in a phase III, prospective, randomized, controlled, double-blind study of 305 subjects at 22 centers in the US.