

SUMMARY BASIS FOR APPROVAL

Submission Tracking Number: 125247/0.0
Biological Product Name: Thrombin, Topical (Human)
Manufacturer: OMRIX biopharmaceuticals Ltd., MDA Blood Bank,
 Sheba Hospital, POB 888, Kiryat Ono 55000, Israel.
Trade Name: EVITHROM

I. INDICATIONS FOR USE

EVITHROM Thrombin Topical (Human) 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 is ineffective or impractical.

EVITHROM Thrombin Topical (Human) may be used in conjunction with an Absorbable Gelatin Sponge, USP.

II. DOSAGE FORM, ROUTE OF ADMINISTRATION AND RECOMMENDED DOSAGE

A. Dosage Form

EVITHROM is formulated as a non-pyrogenic, sterile solution, pH 6.8-7.2, containing highly purified human thrombin (800-1200 IU/ml) for the activation of clotting. EVITHROM is available in vials containing 2 ml, 5 ml or 20 ml frozen solution. Biological potency of thrombin is determined by an *in vitro* assay referenced to the World Health Organization International Standard for Thrombin Concentrates. The final product is formulated with approximately ----- calcium chloride, ----- human albumin, ---- (w/v) mannitol, ----- acetate and contains no preservatives or animal derived components.

B. Route of Administration

For topical use only. DO NOT INJECT.

The following precautions must be taken when using EVITHROM:

- EVITHROM must not be injected directly into the circulatory system.
- EVITHROM must not be used in individuals known to have anaphylactic or severe systemic reaction to human blood products.
- EVITHROM must not be used for the treatment of severe or brisk arterial bleeding.

EVITHROM may be thawed in a refrigerator (2°C to 8°C) for 1 day, at room temperature (20°C to 25°C) for 1 hour or at 37°C for up to 10 minutes (for 2 ml or 5 ml fill size; 20 ml fill size will thaw within 30 min.) just prior to planned use. Thawing temperature must not exceed 37°C. Once thawed EVITHROM should not be re-frozen. EVITHROM may be

transferred by the circulating nurse to the operating nurse in the sterile operating field for product application.

EVITHROM is used topically and should be applied on the surface of bleeding tissue only. EVITHROM may be used alone or in conjunction with an Absorbable Gelatin Sponge, USP.

When applied alone the target surface should be sponged or suctioned to ensure that it is free of blood. The surface may be flooded with EVITHROM using a sterile syringe and small gauge needle. After treatment, sponging of the clot should be avoided to assure that it remains securely in place.

If EVITHROM is to be used in conjunction with Absorbable Gelatin Sponge, USP, the solution should be transferred to a sterile container using aseptic techniques. The gelatin sponge of desired shape should be immersed in the EVITHROM solution and vigorously kneaded with moistened gloved fingers until all air is expelled and it can be returned to its original size and shape. The saturated sponge is kept in place with gauze or cotton pledget using moderate pressure until hemostasis is achieved.

C. Recommended Dosage

The amount of EVITHROM required depends upon the area of tissue to be treated and the method of application. In clinical studies volumes up to 10 ml were used in conjunction with Absorbable Gelatin Sponge, USP.

III. MANUFACTURING AND CONTROLS

A. Manufacturing

EVITHROM is made from pooled human Source Plasma obtained from US licensed plasma collection centers.

Individual plasma units obtained for production of EVITHROM are tested by FDA-licensed serological tests for HBsAg, HIV 1 & 2 Ab and HCV Ab as well as FDA-licensed Nucleic Acid Testing (NAT) methods for HCV and HIV-1. Each plasma unit must be non-reactive (negative) in all tests.

Additionally, the plasma is tested by NAT for HAV and HBV and must be negative. Since the effectiveness of these test methods in detecting low levels of viral material is still under investigation, the significance of a negative result for these viruses is unknown. NAT for parvovirus B19 is also performed and the level of contamination is not permitted to exceed 10,000 copies/ml. This limit is applied to restrict the viral load of parvovirus B19 in the starting plasma pool.

In addition to the screening of plasma units, each manufacturing pool is tested for HBsAg, HIV-1 & 2 Ab, HCV Ab, and for HCV NAT. Manufacturing pool testing, however, is of lower sensitivity than individual unit testing.

EVITHROM is manufactured by chromatographic purification of prothrombin from cryo-poor plasma followed by activation with calcium chloride. The manufacturing process

includes two targeted steps for inactivation or removal of viruses. The first of these is treatment with a solvent/detergent (S/D) mixture (1% tri-n-butyl phosphate, 1% Triton X-100) for 6 hours at 26°C to inactivate lipid enveloped viruses. The S/D reagents are removed by cation exchange chromatography. Mannitol and human albumin are used to stabilize the solution, which undergoes nanofiltration for removal of both enveloped and non-enveloped viruses. After nanofiltration, the solution is formulated with calcium chloride, sterile filtered and aseptically filled and frozen.

Final Container Testing: Final product release tests are performed on every lot of EVITHROM. In addition to required tests for General Safety (21 CFR § 610.11) and Sterility (21 CFR § 610.12), the following tests are performed: appearance, thrombin potency, -----, calcium, human albumin, mannitol, acetate, tri-n-butyl phosphate, triton X-100, pH and -----.

B. Validation

Validation of Systems and Equipment: Utility systems, manufacturing equipment, manufacturing processes and analytical methodologies used in the production of EVITHROM have been validated according to established written procedures. Procedures are in place to ensure routine maintenance of equipment, specified monitoring of environmental conditions and quality oversight within the production facilities.

Virus Inactivation/Removal Studies: The manufacturing process for EVITHROM includes two distinct virus inactivation/removal steps. The capability of each virus inactivation/removal step was quantified during virus spiking studies. The results (expressed as log₁₀ reduction factors) are summarized in the following table.

Table 1: Virus Inactivation/removal: Log₁₀ Reduction Factors

Virus	HIV-1	SBV	BVDV	PRV	EMCV	HAV	CPV
	Reduction factor (log₁₀)						
S/D Treatment	>5.82	> 5.31	>4.74	>4.25	Not Done	Not Done	0.0
Nanofiltration	>4.36	>5.32	Not Done	>5.47	6.37	6.95	5.85
Global Reduction Factor	>10.18	>10.63	>4.74	>9.72	6.37	6.95	5.85

HIV-1: Human Immunodeficiency Virus Type 1

SBV: Sindbis Virus

BVDV: Bovine Viral Diarrhea Virus

PRV: Pseudorabies Virus

EMCV: Encephalomyocarditis virus

HAV: Hepatitis A Virus

CPV: Canine Parvovirus

C. Stability

EVITHROM has a labeled shelf life of 24 months when stored at ≤-18°C. Within the 24 month shelf life, EVITHROM may be stored for up to 30 days at 2-8°C.

Stability studies for EVITHROM were performed at -18±2°C for up to 24 months (real-time), at 2-8°C for up to 30 days following storage at -18±2°C for 2 years (accelerated,

worst case scenario) or after thawing and storage at room temperature for up to 24 hr. Stability studies included three lots of each fill-size. Statistical analysis of results for Thrombin potency supported the labeled storage condition.

D. Labeling

The physician package insert (full prescribing information), container and package labels are in compliance with 21 CFR 201 Subparts A and B and 21 CFR § 610.60 to § 610.62. The trade name EVITHROM is not known to conflict with the trademark of any other biological product.

E. Establishment

All processes involved in the manufacture, packaging, labeling, and holding of EVITHROM are performed at Omrix biopharmaceuticals, Ltd., MDA Blood Bank, Sheba Hospital, Ramat Gan, 52621 Israel, U.S. license No. 1603.

Establishment Inspection: A pre-license inspection of Omrix biopharmaceuticals, Ltd. production facilities at the MDA Blood Bank was performed on October 20-29, 2002 for licensure of EVICEL, Fibrin Sealant (Human). The inspection was performed by personnel from the Center for Biologics Evaluation and Research and Office of Regulatory Affairs. An FDA Form 483 was issued; the firm responded to all observations and their corrective actions were found to be adequate and complete. The pre-license inspection for EVITHROM was waived because the -----
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F. Environmental Assessment

A categorical exclusion from the requirement to prepare an Environmental Assessment was requested under 21 CFR 25.31(c). This request was found to be justifiable.

G. Product Batch/Lot Identification

Each lot of EVITHROM is identified by unique batch and specification numbers. -----
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IV. PHARMACOLOGY/TOXICOLOGY

The pharmacological and toxicological properties of EVITHROM were derived from studies using EVICEL -----
----- Test models, mode of

Pharmacodynamics

During the pharmacological assessment of EVICEL, the velocity of the primary reaction between thrombin and fibrinogen had been shown to be dependent on the concentration of thrombin. A study was performed to determine the thrombin concentration to include in EVICEL for optimum hemostatic activity. Rabbits received standardized liver resections that were treated with sealant containing varying concentrations of thrombin (200 to 1000 IU/ml). Concentration dependent decrease in bleeding time was observed; the thrombin component concentration of 1000 IU/ml proving optimal. -----

Pharmacokinetics

Studies were conducted during the pharmacological assessment of EVICEL in rabbits to evaluate the absorption and elimination of thrombin when applied to the cut surface of the liver resulting from partial hepatectomy. Using ^{125}I -thrombin, it was shown that a slow absorption of biologically inactive peptides resulting from the breakdown of thrombin occurred, reaching a C_{max} in the plasma after ---- hours. At the C_{max} , the plasma concentration represented ----- of the applied dose.

EVITHROM is metabolized and absorbed by the physiological fibrinolytic system in the same way as endogenous thrombin.

Toxicology

EVICEL was classified as non-irritant in the Primary Cutaneous Irritation Test and slightly irritant in the Ocular Irritation test.

Neurotoxicity studies performed with EVITHROM or EVICEL confirmed that intracerebral application of thrombin was not associated with evidence of neurotoxicity.

No toxicological effects due to solvent/detergent reagents [tri-n-butyl phosphate (TnBP) and Triton X-100] used in the virus inactivation procedure are expected since the residual levels are less than $5\mu\text{g/ml}$.

Reproductive studies performed in rats with the combination of TnBP and Triton X-100 at doses up to approximately 600-fold human dose of TnBP ($900\mu\text{g/kg/day}$) and 3000-fold human dose of Triton X-100 ($4500\mu\text{g/kg/day}$) resulted in increased post-implantation loss and an increased number of late resorptions. Other studies performed with combinations of TnBP (300-fold human dose, $450\mu\text{g/kg/day}$) and Triton X-100 (1500-fold human dose, $2250\mu\text{g/kg/day}$) resulted in increased resorption rates, decreased fetal body weights, and an increased number of runts. No embryo-fetal adverse effects were observed at doses up to $300\mu\text{g/kg/day}$ TnBP and $1500\mu\text{g/kg/day}$ Triton X-100, 200-fold and 1000-fold the human dose, respectively.

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

Studies performed in bacteria to determine mutagenicity were negative for human thrombin alone, TnBP alone, or Triton X-100 alone at all concentrations tested. All concentrations of the combination of TnBP and Triton X-100 also tested negative in assays performed to determine mammalian cell mutagenicity, chromosomal aberrations and micronuclei induction.

V. CLINICAL

A. Clinical Efficacy

EVITHROM was compared with bovine thrombin in a phase III, multicenter, prospective, randomized, controlled, double-blinded study of 305 subjects at 22 centers in the US. Subjects undergoing elective cardiovascular, neurologic (spinal) 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. Bovine thrombin and EVITHROM were applied with SURGIFOAM* Absorbable Gelatin Sponge, USP.

Treatment 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 or 3 minutes of product application.

Table 2: Efficacy for Intent to Treat (ITT) population

Time Interval	Treatment Group: # Successes/N (%)		Ratio Human/Bovine	95% CI for Ratio Human/Bovine ^{1,2}
	EVITHROM N=153	Bovine Thrombin N=152		
10 minutes	149/153 (97.4)	148/152 (97.4)	1.00	0.96, 1.05
6 minutes	145/153 (94.8)	141/152 (92.8)	1.02	0.96, 1.09
3 minutes	112/153 (73.2)	110/152 (72.4)	1.01	0.88, 1.16

¹ 95% CI is for the ratio of proportions of success

² For the two treatments to be equivalent, both limits of the confidence interval must have been within (0.80, 1.25)

Table 3: Efficacy at 6 minutes (ITT population)

Surgical Specialty	Treatment Group: # Successes/N (%)		Ratio Human/Bovine	95% CI for Ratio Human/Bovine ^{1,2}
	Human Thrombin	Bovine Thrombin		
Cardiovascular	44/47 (93.6)	38/46 (82.6)	1.13	0.97, 1.36
Neurosurgical (Spine)	60/61 (98.4)	59/60 (98.3)	1.00	0.93, 1.08
General Surgery	41/45 (91.1)	44/46 (95.7)	0.95	0.82, 1.08
Overall	145/153 (94.8)	141/152 (92.8)	1.02	0.96, 1.09

¹95% CI is for the ratio of proportions of success.

²For the two treatments to be equivalent, both limits of the confidence interval must have been within (0.80, 1.25)

At the 6 minute and 10 minute time points, >90% of subjects from all surgeries in both study groups had achieved hemostasis. The following results were documented for the 3 minute time point as stratified by surgery and study treatment: (1) cardiovascular surgery- human thrombin: 61.7%; bovine thrombin: 63.0%, (2) spinal surgery- human thrombin: 83.6%; bovine thrombin: 80.0%, (3) general surgery- human thrombin: 71.1%; bovine thrombin: 71.7%, for an overall ratio of 1.01.

B. Clinical Safety

Anaphylactic reactions may occur in rare cases. No adverse events of this type were reported during the conduct of the clinical trials. Mild reactions can be managed with anti-histamines. Severe hypotensive reactions require immediate intervention using current principles of shock therapy.

In the phase III study of 305 subjects during which EVITHROM (n=153) was compared with bovine thrombin (n=152), occurrence of adverse events was not statistically different between the two study groups. The most common adverse events reported were procedural complications and pruritus. No clinically significant differences were seen in age (< 65 years, > 65 years) or gender subgroup analyses of adverse events. No deaths were reported during the study period. Viral serology was not monitored during the study with EVITHROM; however, no adverse events indicative of infection with transfusion-transmissible adventitious agents were reported.

Table 4: Incidence of Subjects with related adverse events reported in at least 2% of subjects treated with either human or bovine thrombin

System Organ Class/Adverse Event	Thrombin		Total (n=305)
	EVITHROM (n=153)	Bovine (n=152)	
Investigations	11 (7.2%)	14 (9.2%)	25 (8.2%)
Activated partial thromboplastin time increased	4 (2.6%)	8 (5.3%)	12 (3.9%)
International normalized ratio increased	4 (2.6%)	5 (3.3%)	9 (3.0%)
Lymphocyte count decreased	4 (2.6%)	2 (1.3%)	6 (2.0%)
Prothrombin time prolonged	4 (2.6%)	8 (5.3%)	12 (3.9%)
Neutrophil count increased	3 (2.0%)	2 (1.3%)	5 (1.6%)
Skin and Subcutaneous Tissue Disorders	1 (0.7%)	3 (2.0%)	4 (1.3%)
Pruritis	1 (0.7%)	3 (2.0%)	4 (1.3%)
General Disorders and Administration Site Conditions	0	3 (2.0%)	3 (1.0%)
Pyrexia	0	2 (1.3%)	2 (0.7%)

Immunogenicity: In the clinical study, serum samples were collected at baseline and at 5 weeks post-surgery for evaluation of antibodies to bovine thrombin, bovine Factor V/Va, human thrombin, or human Factor V/Va. Samples were collected at both time points for 81.3% of the subjects. The ELISA data were adjudicated by a panel of experts blinded to treatment assignment. After reviewing all data, the panel used an algorithm for assigning outcomes for each antigen: seroconversion negative or seroconversion positive. The protocol did not specify comparative analysis for immunogenicity data; rather, descriptive statistics. The adjudicated results indicated that 3.3% of the subjects treated with EVITHROM had developed antibodies to one of the four antigens vs. 12.7% of subjects treated with bovine thrombin. In the bovine thrombin group, 7.94% of subjects developed antibodies to bovine thrombin and 9.52% of those subjects also developed antibodies to human thrombin. None of the bovine thrombin treated subjects developed antibodies cross-reactive with human Factor V/Va. Furthermore, none of the subjects treated with EVITHROM developed detectable antibodies to human thrombin or to human Factor V/Va. The detection of antibody formation is dependent upon the sensitivity and specificity of the assay. The observed incidence of a positive signal in an assay may be influenced by several factors e.g. timing of sampling, sample handling, concomitant medications or underlying disease.

VI. PACKAGE INSERT

A copy of the physician's package insert (full prescribing information) is attached