SUMMARY BASIS FOR APPROVAL

Submission Tracking Number: 125010/0.0

Biological Product Name: Fibrin Sealant (Human)

Manufacturer: OMRIX biopharmaceuticals Ltd., MDA Blood Bank, Sheba Hospital, POB 888, Kiryat Ono 55000, Israel.

Trade Name: Crosseal™

I. INDICATIONS FOR USE

Crosseal™ Fibrin Sealant (Human) is indicated as an adjunct to hemostasis in patients undergoing liver surgery, when control of bleeding by conventional surgical techniques, including suture, ligature and cautery is ineffective or impractical. Crosseal™ is not indicated for the treatment of massive and brisk arterial bleeding. Crosseal™ is for topical use only; it should never be injected.

Pediatric Use

Of the 216 patients treated in adequate and well-controlled studies of Crosseal™ in liver surgery, eight were pediatric patients. Of these, five were less than 2 years old and three were between 2 and 12 years old. An additional 92 patients under the age of 18 have received Crosseal™ during liver surgery in the UK. Use of Crosseal™ in pediatric patients is supported by these data and by extrapolation of findings for safety and efficacy in adults.

Geriatric Use

Of the total number of subjects in clinical trials of Crosseal™ in liver surgery, 24 were over 65 years of age. Although no overall differences in safety or effectiveness were observed between the elderly and younger patients, greater susceptibility of some older patients to adverse reactions cannot be ruled out.

Pregnancy Category C:

Animal reproduction studies have not been conducted with Crosseal™. It is also not known whether Crosseal™ can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Crosseal™ should be used to treat a pregnant woman only if clearly needed.

II. DOSAGE FORM, ROUTE OF ADMINISTRATION AND RECOMMENDED DOSAGE

Crosseal™ is a single use kit consisting of two packages. The first contains one vial each of frozen sterile solutions of Biological Active Component (BAC) and Thrombin and the second contains a sterile administration device. BAC contains 40-60 mg/ml fibrinogen. Thrombin has an activity of 800-1200 IU/ml.

When the thawed BAC and Thrombin solutions are combined by simultaneous application using the administration device supplied, a fibrin clot is formed through the cleavage of fibrinogen by thrombin.

Dosage

The active components of Crosseal™ (BAC and Thrombin) are available in dosages of 1 ml, 2 ml, or 5 ml each component per kit. Crosseal™ is administered topically by spraying or dripping. A 1 ml Crosseal™ kit is sufficient to cover an area of 20 cm^2. If the hemostatic effect is not complete, a second layer should be applied.

Application of CrossealÔ

The following precautions must be taken when using Crosseal™:

- The BAC and Thrombin components of Crosseal™ must only be administered topically.
- Crosseal™ must not be injected directly into the circulatory system.
- Crosseal™ must not be used in surgical operations where contact with the CSF or dura mater could occur.

Crosseal™ must be applied with the administration device supplied. This device allows for the simultaneous application of equal volumes of the two component solutions and ensures mixing, which is essential for the sealant to achieve optimal efficacy. The device consists of two identical disposable syringes with linked plungers that provide for the delivery of equal volumes of the two solutions through separate lumens of a catheter. The two solutions mix as they are expelled from the catheter.

BAC and Thrombin solutions can be thawed in a refrigerator (2°C to 8°C) for 1 day or at room temperature (20°C to 25°C) for 1 hour just prior to planned use. The sterile solutions and administration device can be transferred by the circulating nurse to the operating nurse in the sterile operating field for device loading and product application. The product should be sprayed or dripped onto the surface of the tissue in short bursts (0.1 –0.2 ml) to form a thin even layer. For application of Crosseal™ by spraying, an air tube is used to connect the administration device to a suitable air supply, regulated at a pressure of 35 to 45 psi. The air passes through a third lumen in the application catheter

and aerosolizes the BAC and Thrombin at the tip of the catheter.

III. MANUFACTURING AND CONTROLS

A. MANUFACTURING

Source plasma for use in the production of BAC and Thrombin is collected according to the requirements of 21 CFR §640.60 (Source Plasma) at FDA-licensed establishments located in the United States. **See also Section V (A), Plasma Safety.**

The human albumin used in the manufacture of Thrombin solution meets all the requirements for Albumin (Human) in 21 CFR §§ 640.80-640.83.

Manufacture of Biological Active Component (BAC) solution

Cryoprecipitate is obtained from frozen plasma by ----------. The cryoprecipitate is treated with aluminum hydroxide gel to adsorb the Vitamin K dependent clotting factors and is then incubated with a solvent detergent (SD) mixture consisting of 1% tri-n-butyl phosphate and 1% Triton X-100 for ---------- to inactivate enveloped viruses (first virus inactivation step).

The solvent detergent (SD) reagents are removed by castor oil extraction and reverse phase chromatography (C-18 column). The preparation is subsequently stabilized by addition of sucrose (1.8 g/g column filtrate) and glycine (0.11 g/g) at a temperature of 37°C. The pH is adjusted to 6.8–7.4. Pasteurization of the stabilized solution is performed at 60±0.5°C for 10 hr. (second virus inactivation step).

After pasteurization, the stabilizers used for heat treatment are removed by diafiltration and the product is concentrated by ultrafiltration. For final formulation, tranexamic acid is added to the BAC as a stabilizer prior to sterile filtration. The filtered BAC solution is filled aseptically in 1 ml, 2 ml, or 5 ml aliquots, frozen at ≤-60 °C and stored at -30±5°C until distribution.

Manufacture of Thrombin solution

Cryo-poor plasma, the starting material for the production of Thrombin, is applied to an anion exchange column for binding of prothrombin and activation into thrombin. The resultant thrombin does not bind to the column and is eluted with calcium chloride.

Thrombin eluted from the anion exchange column undergoes SD treatment for 6 hr. at 26±1°C (first virus inactivation step). The SD reagents are removed by cation exchange chromatography. Mannitol and human albumin are added to the product as stabilizers to a final concentration of 2% (w/w) and 0.2% (w/w), respectively. The stabilized solution is then filtered through a nanofiltration module (second virus clearance step).

The filtrate is formulated with calcium chloride to 40 mM and human albumin to 0.6% prior to sterile filtration. The filtered Thrombin solution is filled aseptically in 1 ml, 2 ml, or 5 ml aliquots, frozen at ≤-60°C and stored at –30±5°C until distribution.

Final Container Testing

Final product release tests are performed on every lot of each component of Crosseal™. In addition to the required tests for General safety (21 CFR § 610.11) and Sterility (21 CFR § 610.12), the following tests are performed:

i) Biological Active Component: Appearance, total protein, fibrinogen, tranexamic acid, arginine hydrochloride, glycine, citrate, tri-n-butyl phosphate, triton X-100, pH, endotoxin and stability of the solution.

ii) Thrombin: Appearance, thrombin potency, total protein, calcium, human albumin, mannitol, acetate, tri-n-butyl phosphate, triton X-100, pH and endotoxin.

Manufacture of the CrosseaÔ Administration Device

The Crosseal™ administration device is a sterile, pyrogen free, single use device which is intended for use in the simultaneous application of the two components of Crosseal™ either by dripping (no air pressure) or by spraying (using a pressure regulator unit, available as a device accessory).

The manufacturer of the Crosseal™ administration device is ----------. The device is assembled, packaged and labeled and ----------.

The Crosseal™ administration device received clearance from the Center for Devices and Radiological Health as a Class II Medical Device (Performance Standards) under section 510(k) of the Federal Food, Drug and Cosmetic Act on 21 March 2003.

B. VALIDATION

Validation of Systems and Equipment

Utility systems, manufacturing equipment, manufacturing processes and analytical methodologies used in the production of Crosseal™ have been validated according to established written procedures. Procedures are in place to ensure the regular maintenance of equipment and the regular monitoring of environmental conditions within the production facilities.

Viral Inactivation/Removal Studies

Virus inactivation/removal studies have been performed for each of the two human plasma-derived components of Crosseal™ (BAC and Thrombin). The manufacturing

process for each component includes two discrete virus inactivation/removal steps and the efficacy of each of these steps was quantified by viral spiking studies. These results (expressed as $\log_{10}$ reduction factors) are summarized in the following tables.

a) BAC

Virus	HIV-1	BVDV	PRV	EMCV	HAV	CPV
	Reduction factor ($\log_{10}$)					
SD Treatment	>4.42	>4.39	>3.96	Not Done	Not Done	0.0
Pasteurization	>4.39	>5.46	Not Done	3.69	2.66	1.33
Global Reduction Factor	**>8.81**	**>9.85**	**>3.96**	**3.69**	**2.66**	**1.33**

b) Thrombin

Virus	HIV-1	SBV	BVDV	PRV	EMCV	HAV	CPV
	Reduction factor ($\log_{10}$)						
SD 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**

C. STABILITY STUDIES

The long-term storage temperature for BAC and Thrombin solutions is ≤-18°C. In addition, the Crosseal™ components can be stored at 2-8°C for up to 30 days. The administration device must be stored at room temperature.

Stability studies have been performed on the two biological components of Crosseal™ as follows:

BAC solution

Primary stability data to support the intended storage conditions and expiry dates of the individual human plasma-derived components were obtained from studies performed at 2-8 °C and –18±2°C. Studies included three lots of each fill-size of BAC (1 ml, 2 ml, and 5 ml).

The study at 2–8°C lasted 12 weeks with all lots meeting the product release specification at the end of the study period. Statistical analysis of the results for clottable protein in BAC support a shelf-life of 30 days at 2–8°C, with all three fill sizes demonstrating consistent stability. In addition, three batches of 5 ml BAC underwent an 'end of shelf-life' study that confirmed the stability of BAC final product for at least 30 days beyond the 24 month product shelf life when stored at 2-8°C.

The study at –18±2°C is ongoing but interim results support a shelf life of 24 months for each of the fill sizes of BAC when stored at –18±2°C.

Thrombin solution

Stability studies for Thrombin solution were performed at 2-8°C and –18±2°C and included three lots of each fill-size.

Statistical analysis of the results for potency of Thrombin solution support a shelf-life of 30 days at 2–8°C, with all three fill sizes demonstrating consistent stability. In addition, three batches of 5 ml Thrombin underwent an 'end of shelf-life' study that confirmed the stability of Thrombin final product for at least 30 days beyond the 24 month product shelf life when stored at 2-8 °C.

The study at –18±2°C is ongoing but interim results support a shelf life of 24 months for each of the fill sizes.

D. LABELING

The package insert and container and package labels are in compliance with 21 CFR §§ 201.57 and 610.60 to 610.62. The trade name Crosseal™ is not known to conflict with the trademark of any other biological product.

E. ESTABLISHMENT

Location associated with the Production of CrosseaÔ

OMRIX biopharmaceuticals Ltd., MDA Blood Bank, Sheba Hospital, Ramat Gan, 52621 Israel, U.S.license No. 1603

Establishment Inspection

A pre-license inspection of the facilities of OMRIX biopharmaceuticals involved in the manufacture of Crosseal™ was performed on October 20 – 29, 2002. 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.

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 BAC and Thrombin is ----------. The expiration dates of the components are determined independently. When the BAC and Thrombin are packaged together, the Crosseal™ kit is ----------.

IV. PHARMACOLOGY/TOXICOLOGY

Pharmacodynamics

Crosseal™ is a plasma-derived fibrin sealant consisting of two separate components that are combined on application. The first component is a concentrated solution of clottable fibrinogen and the second component is a thrombin solution containing $CaCl_2$. When combined, the two preparations rapidly form a clot, reproducing the final stages of the coagulation cascade.

The velocity of the primary reaction between thrombin and fibrinogen has been shown to be dependent on the concentration of thrombin. The concentration of fibrinogen in the BAC component is 40-60 mg/ml. A study was performed to determine the thrombin concentration to include in Crosseal™ for optimum hemostatic activity. Rabbits received standardized liver resections that were treated with sealant containing varying concentrations of thrombin (200 to 1000 IU/ml). A concentration-dependent difference in bleeding time was observed, with a thrombin component concentration of 1000 IU/ml proving to be optimal.

The Thrombin component of Crosseal™ is, therefore, formulated with 1000 IU/ml thrombin which when mixed with BAC in equal volumes results in a final thrombin concentration of ---------- leading to a rapid primary reaction. The $CaCl_2$ concentration in the Thrombin solution is ---------- which, when mixed with equal parts of the BAC component results in a -------- concentration in the final product to facilitate cross-linking of the clot by ----------.

Pharmacokinetics

Studies were conducted in rabbits to evaluate the absorption and elimination of thrombin and tranexamic acid 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. A study using ^{3}H-tranexamic acid showed it to be very quickly absorbed. The ----- was in most cases between ---------- hours, reaching a Cmax of ----------. Ten hours after treatment the elimination from the plasma was complete.

Crosseal™ is metabolized and absorbed by the physiological fibrinolytic system in the same way as an endogenous clot.

Toxicology

Crosseal™ has been classified as non-irritant in the Primary Cutaneous Irritation Test and slightly irritant in the Ocular Irritation test. Neither BAC nor Thrombin solution induces mutagenic effects in the Ames test.

Solvent detergent reagents (tri-n-butyl phosphate and Triton X-100) used in a virus inactivation procedure are controlled in the final product with specified residual levels ----------. Animal studies have shown this level to be non-toxic.

Studies in rabbits have shown that one of the constituents of Crosseal™, tranexamic acid, exerted neurotoxicity when applied directly to the CSF or dura mater.

V. SAFETY

A. PLASMA SAFETY

a) Donor Program

Crosseal™ is prepared from Source Plasma (Human) obtained exclusively from FDA-licensed plasmapheresis centers located in the United States. All new donors undergo a medical examination by a qualified licensed physician (or person trained in assessing donor suitability and operating under the supervision of a physician) prior to the first donation and at annual intervals thereafter. Donor suitability is determined in accordance with CFR 21 § 640.63.

Each unit of plasma is tested for antibodies against HIV 1 & 2 and HCV, for HIV-1 Ag and for HBsAg; all must be non-reactive. In addition, all the units of plasma used for the production of Crosseal™ are tested as minipools for the presence of HAV, HBV, HCV, HIV, and Parvo B19 viruses by Nucleic Acid Testing. The individual plasma units are also tested for syphilis and elevations of ALT.

b) First Time Donors

Donors meeting the above requirements must return within 6 months to donate a subsequent unit that passes all pathogen screening tests in order to become a qualified donor. Plasma obtained from a qualified donor is held in quarantine until that donor returns to the center for repeat donation that passes the panel of screening tests. If the applicant donor does not return, the initial plasma donation is destroyed. Any donor who has not donated within the prior six months is not considered to be a qualified donor.

B. POOL SIZE

Each batch of BAC is manufactured using blood plasma from up to -------- donations and each batch of Thrombin originates from up to -------- donations. Therefore, each kit of Crosseal™ originates from up to -------- individual blood plasma donations.

C. VIRAL SAFETY

See Sections III B, Validation and VI B, Clinical Safety.

VI. CLINICAL

A. CLINICAL EFFICACY

Efficacy of Crosseal™ as an adjunct to hemostasis in patients undergoing liver surgery, when control of bleeding by conventional surgical techniques, including suture, ligature and cautery is ineffective or impractical.

Crosseal™ was evaluated in a pivotal Phase III single-blind, randomized, parallel-group, multi-center study against FDA-approved control topical hemostats in 121 patients undergoing liver resection at 15 centers. Patients were randomized (stratified by surgeon) at the conclusion of the liver resection surgery if general oozing was present that could not be controlled by further surgical methods and a topical hemostat was needed to control the bleeding from the liver surface. For the primary endpoint, time to hemostasis, Crosseal™ was shown to be statistically significantly superior to the control hemostatic agents **(p=0.011 one-sided).** Center effects are to be expected in multicenter studies, particularly in surgical indications. Data from one center, which used a specific control agent, made a major contribution to this result. However, of the sixteen surgeons who treated more than one patient in this study, ten found the time to hemostasis to be equivalent to, or shorter than that achieved with some of the control agents.

Primary Endpoint: Time To Reach Hemostasis	
Crosseal™	FDA-Approved Control Topical Hemostats
5.3 minutes	7.7 minutes
Intent-to-treat analysis; one sided: p = 0.011	

B. CLINICAL SAFETY

Data from a total of 216 patients treated with Crosseal™ during clinical trials in liver surgery or joint replacement surgery indicated no particular safety concerns related to the product. No viral seroconversions occurred. Adverse event frequencies in the Crosseal™ group relative to the control group differed for men and women, for patients in different age groups, and for liver surgery patients who did or did not receive anti-coagulants, however, there were no consistent patterns indicating safety problems in specific patient groups.

The results of these clinical studies are supported by 3 years use of Crosseal™ as a marketed product in over 7000 patients undergoing a variety of surgical procedures. Due to the neurotoxicity of tranexamic acid, contact of Crosseal™ with the CSF, dura mater, brain, or spinal cord should be avoided. Data from animal studies showed no indication

of other safety problems.

Licensing Review Committee

Office	Name/Signature	Date
DH/ HFM-340	Nancy Kirschbaum, Ph.D./	
DH/ HFM-392	Paul Aebersold, Ph.D./	
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DH/ HFM-345	Roman Drews, Ph.D./	
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