

### Carcinogenesis, Mutagenesis and Impairment of Fertility

- Long term animal studies to evaluate the carcinogenic potential of fibrin sealants are not available

### Interactions

- No formal interaction studies have been performed with fibrin sealants
- The fibrinogen concentrate and thrombin solution can get denatured after exposure to solutions containing alcohol, iodine or heavy metals (e.g. antiseptic solutions). Such substances should be removed to the greatest possible extent before applying the sealant
- Due to their low pH, oxycellulose-containing preparations may reduce the efficacy of Fibrin Sealant and should not be used as carrier materials
- Aprotinin solution is known to be incompatible with heparin if given intravenously. Such interactions are not reported with local applications containing Aprotinin. Most corticosteroids, nutrient solutions containing Aminoacid, fat, antibiotic solutions are known to react with proteins including Aprotinin. Aprotinin, in the presence of heparin, has also been found to prolong the activated clotting time.

### Pregnancy and Lactation

- Experimental animal studies are insufficient to assess the safety with respect to reproduction, development of the embryo or foetus, the course of gestation and peri- and postnatal development
- Pregnancy Category C. The safety of the sealant for use in human pregnancy or breastfeeding has not been established in controlled clinical trials. It is also not known whether *ReliSeal™* can affect the reproduction capacity

- Thus, fibrin sealant should be administered to pregnant and lactating women only if clearly indicated

### Paediatric & Geriatric population

- Safety and effectiveness of fibrin sealants in the above patient population has not yet been systematically studied

### OPERATING INSTRUCTIONS & APPLICATION

Kindly refer to the "*ReliSeal™* usage sheet" with the procedure for reconstitution and application which has been enclosed with the kit

### Dosage

- The volume of the sealant to be applied and the frequency of application should always be oriented towards the underlying clinical needs for the patient including, but not limited to, the type of surgical intervention, the size of the area of intended application and the number of applications.

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### VIRAL INACTIVATION

The manufacturing process for *ReliSeal™* uses plasma collected from approved blood banks where the donors are screened for their history as per guidelines laid down by the regulatory authorities. Their blood is screened for the mandatory infectious diseases. The plasma is further tested prior to manufacturing of *ReliSeal™* for freedom from HIV 1&2 antibodies, HBsAg. After manufacturing, the product is tested by suitable methods to show freedom from viruses like HIV, Hep B, HCV, Parvo virus and HAV. The manufacturing procedure incorporates Solvent Detergent Technology which inactivates lipid coated viruses. Although all possible care and steps have been taken to make the product safe at multiple levels, there is a remote probability that unknown infectious agents may be present in these products.

The manufacturing process with the incorporated viral inactivation procedures have been validated as per recommendations and guidelines provided by the committee for proprietary medicinal products (CPMP guidelines). Validation studies were conducted using starting plasma samples spiked with model viruses [Table 1] to represent the worst case conditions. Appropriate samples were drawn for viral titre determinations from manufacturing intermediates.

Model Virus	Genus	Enveloped	Size	Log Reduction achieved after inactivation treatment	
				Fibrinogen	Thrombin
New Castle Disease Virus	Paramyxovirus	Yes	150-300 nm	8	3.3
Infectious Bovine Rhino Trachitis virus	Adenovirus	Yes	85-150 nm	4	2.2
Infectious Canine Hepatitis Virus*	Herpesvirus	No	70-80 nm	1	1.5

\*Negative Control.

Table 1 shows that enveloped viruses showed significant log reduction after the inactivation treatment. The above two lipid coated model viruses exhibit wide variations in physicochemical properties and successful log reduction ensures that our procedures will always inactivate lipid coated viruses such as HIV, HBV, & HCV.

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- The initial volume of the sealant to be applied at a chosen anatomic site or target surface area should be sufficient to entirely cover the intended application area. The application can be repeated, if necessary. For some procedures (e.g. liver trauma, or the sealing of large burn surfaces), larger volumes may be required

- 1 ml of fibrin sealant is sufficient to seal 8 cm<sup>2</sup> area. However, this is only a guideline. The clotting time of fibrinogen depends on the thrombin concentration. The clotting time can be controlled suitably by adjusting the thrombin concentration.

### Note:

- The reconstituted components in solution of *ReliSeal™* should be used by applying locally as soon as possible and not later than 4 hrs. Store at room temperature. Do not refrigerate.

- Partially used vials should be discarded

- Adequate training of surgical and nursing staff prior to the use of the product is recommended

### Overdosage

No case of overdose has been reported with the use of fibrin sealants.

### STORAGE

The lyophilised powder is to be stored between +2°C and +8°C (35°F and 46°F), protected from light. *ReliSeal™* should not be used after the expiry date indicated on the container and package labels. Keep out of the reach of children.

### PRESENTATION

Fibrin Sealant, *ReliSeal™* 1 ml and 0.5 ml kit.

The pack contains:

- 1 vial [Yellow Capped] of Freeze Dried Human Fibrinogen B.P.
- 1 vial [Blue Capped] of Freeze Dried Human Thrombin
- 1 vial [Red Capped] of Aprotinin Solution (Bovine)
- 1 x 5 ml plastic ampoule of sterile water for injection I.P.
- 4 x 2 ml graduated sterile syringes with four disposable needles (21G) and two blunt application needles (20G)
- 1 *ReliSeal™* Applicator with two mixing chambers and one plunger guide

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Table 2 gives the summary of tests conducted on *ReliSeal™* from raw material to finished product stage to rule out transmissible infections

Viruses	PCR	Antigen	Antibody
HIV I & II	✓	-	✓
HBV	✓	✓	-
HCV	✓	-	✓
HAV	✓	-	-
Parvo B <sub>19</sub>	✓	-	-

### PHARMACOLOGY

#### Pharmacodynamics

Pharmacotherapeutic group; local hemostatics. "Hemostatics" are any agents, mechanical or chemical that arrest bleeding. They are used to control hemorrhage from minute vessels or tissues by stopping bleeding or by forming of a clot.

The fibrin adhesion system initiates the last phase of physiological blood coagulation. Conversion of fibrinogen to fibrin monomers by thrombin and cross linking of fibrin monomers to fibrin polymers by factor XIII and calcium leads to clot formation. As wound healing progresses, increased fibrinolytic activity is induced by plasmin and decomposition of fibrin to fibrin degradation products is initiated. Proteolytic degradation of fibrin is inhibited by Aprotinin (an inhibitor of proteases including plasmin). Released Aprotinin and its metabolites are eliminated by the kidney.

#### Pharmacokinetics

Pharmacokinetic studies in different species of laboratory animals with fibrin sealants have shown that they are metabolized in the same way as endogenous fibrin by fibrinolysis and phagocytosis<sup>5</sup>.

#### Mechanism of action

The action of *ReliSeal™* simulates key features of the physiological blood clotting mechanism. The fibrinogen solution, which also contains Factor XIII and bovine Aprotinin (a Fibrinolysis inhibitor) when applied to the wound area along with a solution of thrombin, and calcium chloride, a fibrin clot is formed through cleavage of fibrinogen by thrombin. Factor XIII, activated by thrombin, catalyses the formation of cross-links within the fibrin clot and a stable clot is formed at the site of application. Factor XIII also catalyses the covalent linkage of the naturally existing antifibrinolytic agent  $\epsilon$ -aminocaproic acid to fibrin, protecting the clot against plasmin degradation. This cross-linking helps increase the mechanical strength of the fibrin clot and retard proteolytic degradation<sup>1</sup>. Aprotinin, an effective antifibrinolytic agent acts by delaying the rapid plasmin-mediated lysis of the fibrin clot.

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It can also play a significant role in maintaining the fibrin seal, prolonging hemostasis and stabilizing the clot.

The locally applied mixture quickly sets to form a milky white to translucent mass, which continues to gain in strength within two hours following application. In the course of wound healing, the sealant is completely absorbed.

### CLINICAL STUDIES<sup>7,8,12</sup>

Numerous clinical studies investigating the safety and efficacy of established fibrin sealants as a hemostatic and biodegradable tissue glue in various fields of surgery have been reported. A number of these were controlled studies in fields, including orthopaedic surgery, abdominal surgery, urology and cardiovascular surgery. Use of the sealant has invariably shown superior results in the groups treated as against the untreated controls who underwent the same types of surgery. These results were attributable to effective hemostasis and therefore, resulting in reduced blood loss, a tighter sealing of sutures preventing leakages or a fast and uncomplicated healing of the surgical wound.

Fibrin sealant kits support hemostasis in patients with coagulopathies undergoing surgery where excessive bleeding is controlled by supplementing the deficient factors, although in such cases, the routine line of treatment of replacing the deficient factors will be the basis of therapy to prevent excessive blood loss. The use of fibrin sealants is not to be resorted to as the only line of treatment in congenital deficiencies of clotting factors. Physicians are requested to give the proper dose of factors as indicated. The mainstay of fibrin sealant use, however, is in patients without pre-existing coagulation disturbance, who require major surgery or experience major trauma.

### INDICATIONS

Fibrin Sealants can be used locally as supportive treatment in all surgical disciplines to achieve hemostasis, suture support and tissue adhesion/sealing.

### CONTRAINDICATIONS

- Injection into the nasal mucosa as severe allergic-anaphylactic reactions have been reported
- Intravascular application of the two components either individually or when combined, as unintentional application may lead to thromboembolic complications
- In patients with known allergic reaction to bovine Aprotinin or any constituent of the preparation
- For the treatment of massive and brisk arterial bleeding

### ADVERSE REACTIONS

- After repeated administration and/or in patients with a history of hypersensitivity against bovine protein (Aprotinin) allergic or anaphylactic reactions (in rare cases) can occur. Hypersensitivity or allergic reactions may include angioedema, burning and stinging at the application site, bronchospasm, chills, flushing, generalized urticaria, headache, hives, hypotension, lethargy,

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For the use of a Registered Medical Practitioner or a Hospital only

Fibrin Sealant Kit B.P.

*ReliSeal™*

### DESCRIPTION

*ReliSeal™*, fibrin sealant kit contains coagulation factors and acts as a local hemostatic<sup>1</sup>. The reconstituted components of *ReliSeal™* are mixed just at the site of application of the recipient surface by specially designed *ReliSeal™* Applicator. The resultant mixture simulates the natural physiological phenomenon of blood clotting at the bleeding site and forms a firm viscous clot. Thus the formed clot acts like a seal<sup>2</sup> to arrest bleeding or glue tissues<sup>3</sup>. The fibrin clot also supports wound-healing process<sup>4,5</sup>. It gets absorbed over several days to weeks by the naturally occurring endogenous fibrinolytic enzymes.

### COMPOSITION

The Fibrin Sealant Kit (*ReliSeal™*) contains the following two major components in separate vials:

1. Freeze Dried Human Fibrinogen

2. Freeze Dried Human Thrombin

No antimicrobial preservative is added in any of the components

The fibrin sealant kit also contains:

- A) Aprotinin solution (Bovine) as a sterile solution containing Aprotinin B.P., 1500 kallikrein inhibitor units (kiu)/ml and 1500 kallikrein inhibitor units (kiu)/ml for 1 ml and 0.5 ml kit respectively.

- B) 1 x 5 ml ampoule of sterile water for injection I.P. (WFI)

- C) 4 x 2 ml syringes for reconstitution & application; 4 x 21G sterile needles for aspiration of the two components; 2 x 20G blunt application needles

- D) *ReliSeal™* Applicator with two mixing chambers and one plunger guide

*ReliSeal™* 1 ml / 0.5 ml kit contains:

- I) Component I - Freeze dried Fibrinogen prepared from human blood plasma

- I) Component II - Freeze dried Thrombin prepared from human blood plasma

- I) Aprotinin - Bovine Source

Kit	Fibrinogen: not less than	Thrombin	Aprotinin
1 ml / 0.5 ml	40 mg / 20mg	500 IU / 250 IU	3000 kiu / 1500 kiu

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nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing. Should the symptoms require treatment, the clinician should follow the guidelines of modern therapy, e.g. administration of antihistamines, corticoids, and/or adrenaline.

- Accidental intravenous injection could lead to thromboembolic event and disseminated intravascular coagulation (DIC) and there is also a risk of anaphylactic reaction.

### WARNING AND PRECAUTIONS

#### General

- Since *ReliSeal™* has been prepared from human plasma, the risk of transmission of infectious diseases cannot be totally excluded. The risk of transmission of infective agents is however reduced by:

- Selection by screening of individual donations and plasma pools for HBsAg and antibodies to HIV, HCV.

- Retesting of plasma pools

- Inactivation by well known procedure which is considered effective against enveloped viruses like HIV, HCV and HBV

- For local applications only. Do not apply intravascularly

- The needles should not be reused as the residual thrombin can activate clotting process rendering sealant ineffective and useless

- Do not try to save the reconstituted material for longer than the prescribed time.

- Before administration of *ReliSeal™*, care is to be taken that parts of the body outside the desired application area are sufficiently protected (covered) to prevent tissue adhesion at undesired sites

- As with any protein product, allergic type hypersensitivity reactions are possible<sup>18</sup>. On the appearance of the signs and symptoms, the administration has to be discontinued immediately and not to be re-applied

- In case of shock, the current medical standards for shock treatment should be observed

- Administration in the endoscopic treatment of gastrointestinal bleedings can cause tissue damage, which can lead to formation of intramural haematoma. Abdominal pain, nausea, or vomiting within 1 to 3 days after such endoscopic treatment can constitute symptoms of intramural haematoma.

- In order to avoid excess formation of granulation tissue and slow absorption of *ReliSeal™*, only apply thin layer of *ReliSeal™*

- In the interest of patients, it is recommended that, the physician discusses the risks and benefits of this product every time fibrin sealant is administered

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