For the use of a Registered Medical Practitioner or a Hospital only
For Intravenous injection or infusion only

Human Fibrinogen EP, 1 G

Fibrogen-I™

Freeze Dried Powder, Manufactured From Human Plasma

QUALITATIVE AND QUANTITATIVE COMPOSITION

Fibrogen-I™ is presented as a powder for injection or infusion for intravenous administration containing 1 gm human fibrinogen per vial.
The product contains 20 mg/ml human fibrinogen after reconstitution with 50 ml of sterile water for injections for Fibrogen-I™ 1 gm.
The content of clottable fibrinogen is determined according to Ph. Eur. monograph for human fibrinogen.

Composition:

Each package contains 1 vial with:
1725 – 3110 mg dried powder out of which
700 – 1300 mg Fibrinogen

Human Albumin	400 - 700 mg
L- Arginine Hcl	375 - 660 mg
Sodium Chloride	200 - 350 mg
Sodium Citrate	50 – 100 mg

Excipients recognized to have a known effect: Sodium up to 134.44 mg (5.85 mmol) per 1g of Fibrinogen.

PHARMACEUTICAL FORM

Freeze dried white powder.

CLINICAL PARTICULARS

Therapeutic indication

Therapy and prophylaxis of haemorrhagic diatheses in:

- Congenital hypo-, dys- or afibrinogenaemia
- Acquired hypo fibrinogenaemia resulting from
- Disorders of synthesis in cases of severe liver parenchyma damage
- Increased intravascular consumption e.g. as a result of disseminated intravascular coagulation, hyperfibrinolysis
- Increased loss

The most important clinical pictures associated with a defibrination syndrome are:
Obstetrical complications, acute leukaemia especially promyelocytic leukaemia, liver cirrhosis, intoxications, extensive injuries, haemolysis after transfusion errors, operative interventions, infections, sepsis, all forms of shock as well as tumors especially in the lung, pancreas, uterus, and prostate.

Posology and method of administration

Treatment should be initiated under the supervision of a physician experienced in the treatment of coagulation disorders.

Posology

The dosage and duration of the substitution therapy depend on the severity of the disorder, location and extent of bleeding and the patient's clinical condition.
The (functional) fibrinogen level should be determined in order to calculate individual dosage and the amount and frequency of administration should be determined on an individual patient basis by regular measurement of plasma fibrinogen level and continuous monitoring of the clinical condition of the patient and other replacement therapies used.
Normal plasma fibrinogen level is in the range of 1.5 – 4.5 g/l. The critical plasma fibrinogen level below which haemorrhages may occur is approximately 0.5 – 1.0 g/l.
In case of major surgical intervention, precise monitoring of replacement therapy by coagulation assays is essential.
1. Prophylaxis in patients with congenital hypo-, dys- or afibrinogenaemia and known bleeding tendency.
To prevent excessive bleeding during surgical procedures, prophylactic treatment is recommended to raise fibrinogen levels to 1 g/l and maintain fibrinogen at this level until haemostasis is secure and above 0.5 g/l until wound healing is complete.
In case of surgical procedures or treatment of a bleeding episode, the dose should be calculated as follows:
Initial Dose: If the patients Fibrinogen level is not known, the recommended dose is 70 mg per kg of body weight(bw)administered intravenously.
Subsequent Dose: The target level (1 g/l) for minor events(e.g. epistaxis, intramuscular bleeding or menorrhagia) should be maintained for at least three days. The target level (1.5 g/l) for major events(e.g. head trauma or intracranial haemorrhage) should be maintained for seven days.

$$\text{Dose of fibrinogen (mg/kg body weight)} = \frac{\text{[Target level (g/l) - measured level (g/l)]}}{\text{0.017 (g/l per mg/kg body weight)}}$$

Furthermore, the amount to be administered and the frequency of application of Fibrogen-I™ should always be oriented to the degree of bleeding and the clinical efficacy in the individual case.
In case of major surgical intervention, precise monitoring of replacement therapy by coagulation assays is essential.
The biological half-life of fibrinogen is 3-4 days. Thus, in the absence of consumption, repeated treatment with human fibrinogen is not usually required. Given the accumulation that occurs in case of repeated administration for a prophylactic use, the dose and the frequency should be determined according to the therapeutic goals of the physician for a given patient.
2. Treatment of bleeding

Adults

For perioperative bleeding generally 2 g (or 30 mg/kg body weight) is administered, with subsequent infusions as required. In case of severe haemorrhages i.e. obstetric use / abruption placenta, large amounts (4 – 8 g) of fibrinogen may be required.

Children

Limited data from clinical studies regarding the dosage of fibrinogen in children are available. The dosage should be determined according to the body weight and clinical need but is usually 20-30 mg/kg.

Method of Administration

Intravenous injection or infusion. The injection or infusion rate should not exceed approx. 5 ml per minute.

Contraindications

Hypersensitivity to the active substances or to any of the excipients.
Manifest thrombosis or myocardial infarction, except in cases of life-threatening haemorrhages.

Special warnings and special precautions for use

There is a risk of thrombosis when patients with congenital deficiency are treated with human fibrinogen, particularly with high dose or repeated dosing. Patients given human fibrinogen should be observed closely for signs or symptoms of thrombosis.
In patients with a history of coronary heart disease or myocardial infarction, in patients with liver disease, in pre- or post-operative patients, in neonates, or in patients at risk of thromboembolic events or disseminated intravascular coagulation, the potential benefit of treatment with human plasma fibrinogen should be weighed against the risk of thromboembolic complications. Caution and close monitoring should also be performed.
Generally in case of bleeding the condition of the coagulation system should be observed with appropriate diagnostic assays.
For the treatment of acquired fibrinogen deficiency, particularly in the case of disseminated intravascular coagulation and liver disease, attention should be paid to that there is no isolated deficiency of fibrinogen, but deficiency of all coagulation factors and inhibitors is usual. Therefore as first line therapy a balanced replacement with fresh frozen plasma or specific factor and inhibitor products should be taken into account. Careful monitoring of the coagulation system is necessary.

Front Side

If allergic or anaphylactic-type reactions occur, the injection/infusion should be stopped immediately. In case of anaphylactic shock, standard medical treatment for shock should be implemented.
In the case of replacement therapy with coagulation factors in other congenital deficiencies, antibody reactions have been observed, but there is currently no data with fibrinogen.

Virus safety

Collected blood plasma used for manufacturing of Fibrogen-I™, screened for the mandatory infectious diseases. Only on being declared nonreactive for HBsAg, HCV, HIV I & II antibodies and negative for HIV I & II, HCV, HBV by NAT the plasma is used for processing.
The manufacturing procedure incorporates two dedicated orthogonal viral clearance steps ensuring viral safety of the product. This includes solvent detergent treatment and dried heat treatment.
The drug product is also tested for viral markers like HBV, HIV I & II & HCV. Multiple chromatography steps have been incorporated for assurance of product safety. The process parameters, characterizations and final product quality are designed such, that they meet the regulatory requirements. Fibrogen- I™ contains no preservative and is free from blood group antibodies.
Appropriate vaccination (hepatitis A and hepatitis B) should be considered for patients in regular/repeated receipt of human fibrinogen products.
It is strongly recommended that every time that product is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

Interaction with other medicinal products and other forms of interaction

No interactions of human plasma fibrinogen products with other medicinal products are known.

Fertility, pregnancy and lactation

Pregnancy

Animal reproduction studies have not been conducted. Since the active substance is of human origin, it is catabolized in the same manner as the patient's own protein. These physiological constituents of the human blood are not expected to induce adverse effects on reproduction or on the fetus.
The safety of human plasma fibrinogen products for use in human pregnancy has not been established in controlled clinical trials.
Clinical experience with fibrinogen products in the treatment of obstetric complications suggests that no harmful effects on the course of the pregnancy or health of the fetus or the neonate are to be expected.

Lactation

It is unknown whether fibrinogen products is excreted in human milk. The safety of human plasma fibrinogen products for use during lactation has not been established in controlled clinical trials.
A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from fibrinogen products therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

There are no data regarding effects of fibrinogen products on fertility.

Effects on ability to drive and use machines

Fibrinogen products has no influence on the ability to drive and use machines

Side Effects

Allergic or anaphylactic type reactions (such as generalized urticaria, rash, fall in blood pressure, dyspnoea), nausea, vomiting, chills, pyrexia, cough, - thromboembolic episodes. (including myocardial infarction, pulmonary embolism and arterial thrombosis)

Overdose

In order to avoid over dosage, regular monitoring of the plasma level of fibrinogen during therapy is indicated.
In case of over dosage, the risk of development of thromboembolic complications is enhanced.

Pharmacodynamic properties

Human fibrinogen (coagulation factor I), in the presence of thrombin, activated coagulation factor XIII (factor XIII a) and calcium ions, is converted into a stable and elastic three dimensional fibrin haemostatic clot.
The administration of human fibrinogen provides an increase in plasma fibrinogen level and can temporarily correct the coagulation defect of patients with fibrinogen deficiency.

Instructions for use, handling and disposal

General instructions

- Reconstitution and withdrawal should be carried out under aseptic conditions.
- Reconstituted products should be inspected visually for particulate matter and discoloration prior to administration.
- The solution should be almost colourless to yellowish, clear to slightly opalescent and of neutral pH. Do not use solutions that are cloudy or have deposits.
- **Reconstitution**
- Warm both the solvent and the powder in unopened vials to room or body temperature (not above 37 °C).
- Fibrogen-I™ should be reconstituted with 50 ml of sterile water for injection.
- Gently swirl the vial until the powder is reconstituted and the solution is ready for administration.
- Avoid strong shaking which causes formation of foam. The powder should be completely reconstituted within 30 minutes at 20°C - 25°C.
- Reconstituted product should be administered immediately by a separate injection / infusion line.
- From a microbiological point of view the product should be used immediately following reconstitution.
- However, if it is not administered immediately, the reconstituted solution can be stored up to 8 hours below 25°C. Dispose of unused solution appropriately.
- The reconstituted product should not be stored in the refrigerator.
- Take care that no blood enters syringes filled with product.
- Use Syringe filter for administration.
- Do not use if gel or precipitate is observed when reconstituted.
- Any unused product or waste material should be disposed of in accordance with local requirements.

Incompatibilities

This medicinal product must not be mixed with other medicinal products, diluents, or solvents except solution for reconstitution. A standard infusion set is recommended for intravenous application of the reconstituted solution at room temperature.

Shelf life

24 months from the manufacturing date.
Do not use after expiry date.

PACKING UNIT

Injection is supplied in sterile freeze dried powder form in a single dose vial of colorless glass (USP/EP Type I) sealed with a latex-free bromobutyl rubber stopper, aluminium cap and plastic disc.

STORAGE CONDITION

Store between 2°C and 8 °C in the closed carton to protect it from light.
Do not freeze.
Keep out of the reach and sight of children.
Report suspected adverse reaction at: Hemofluidsafety@intaspharma.com
Date of preparation: 11-Mar-2020
Manufactured & Marketed by:

INTAS PHARMACEUTICALS LTD.
Plot No. 496/1/A&B, Sarkhej - Bavla Highway,
Village: Matoda, Taluka: Sanand, Ahmedabad-382 213.
Gujarat. (INDIA)

AW-050-01

Back Side

Reason for revision : CBL/CCF/2020/0091						Artwork No.: AW-050-01	
Supersedes No.: AW-050-00							
	Prepared by	Reviewed by					Approved by
Department	QA	Production	Regulatory	Marketing	Medical	QA	QA
Sign							
Date							
Name							
Designation							

Product Name: Fibrogen- I Leaflet
Size: 130 x 220 mm
Colour: Pantone Black
110320

Fold size: ~ 65 mm x ~ 27.5 mm
No. of Fold : 4
Type of Paper / Board: Maplitho
GSM of Paper: 50 gsm ± 10 %