

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

FibCLOT 1.5 g. Powder and solvent for solution for injection/infusion.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

human fibrinogen

Each vial of FibCLOT contains nominally 1.5 g of human fibrinogen.

After reconstitution with 100 mL of solvent (water for injections), FibCLOT contains nominally 15 mg/mL of human fibrinogen.

The potency is determined according to the European Pharmacopoeia monograph for human fibrinogen.

Produced from the plasma of human donors.

Excipients with known effect:

Contains up to 69 mg (3 mmol) sodium per vial.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection/infusion.

White or yellowish powder or friable solid in a vial.

Solvent: clear and colourless solution.

This product remains stable after dry heat treatment in the range of pH of 6.5-7.5.

The osmolality of the product is between 450-550 mOsmol/kg.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment and perioperative prophylaxis of bleeding in patients with congenital hypo- or afibrinogenaemia with bleeding tendency. FibCLOT is indicated in all age groups.

4.2 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. In congenital hypo- or afibrinogenaemia, 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.

Treatment of bleeding and prophylaxis in patients with congenital hypo- or afibrinogenaemia and known bleeding tendency.

To treat nonsurgical bleeding episodes, it is recommended to raise fibrinogen levels to 1 g/L and maintain fibrinogen at this level until haemostasis is controlled and above 0.5 g/L until healing is complete.

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 controlled and above 0.5 g/L until wound healing is complete.

In case of surgical procedure or treatment of a nonsurgical bleeding, the dose should be calculated as follows:

$\text{Dose (g)} = [\text{target level (g/L)} - \text{baseline level (g/L)}] \times 1/\text{recovery (g/L)/(g/kg)} \times \text{body weight (kg)}$
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The ratio '1/recovery' is defined from patient's recovery* (see section 5.2), or if recovery is unknown:

- 0.053 (g/kg)/(g/L) for children and adolescents <40 kg body weight
- 0.043 (g/kg)/(g/L) for adults and adolescents ≥ 40kg body weight.

* Example for patient's recovery and dosing calculation

For a 60 kg patient with undetectable baseline fibrinogen level and fibrinogen increase to 1.20 g/L 1 hour after infusion of 0.060 g per kg of FibCLOT:

- Patient's recovery calculation:

$$1.20 \text{ (g/L)} / 0.060 \text{ (g/kg)} = 20.0 \text{ (g/L)/(g/kg)}$$

- Dose calculation for an increase to 1.0 g/L:

$$1.0 \text{ g/L} \times 1 / 20.0 \text{ (g/L)/(g/kg)} [\text{or } 0.050 \text{ (g/kg)/(g/L)}] \times 60 \text{ kg} = 3 \text{ g.}$$

In case of an emergency situation when the baseline fibrinogen level is not known, the recommended initial dose is 0.05 g per kg of body weight administered intravenously in adults and adolescents ≥ 40 kg body weight, and 0.06 g per kg of body weight in paediatric patients < 40 kg body weight.

Subsequent posology (doses and frequency of injections) should be adapted based on the patient's clinical status and laboratory results.

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.

Paediatric population

Data show that the *in vivo* recovery and half-life in children and adolescents < 40 kg body weight is lower than the one in adults and adolescents ≥ 40 kg body weight (see section 5.2). Therefore, adapted recoveries should be used to calculate the FibCLOT dose in the respective body weight groups when the individual patient's recovery is unknown. It can be expected that a body weight of < 40 kg covers the age range from birth up to about 12 years old. The posology (doses and frequency of injections) should be adapted based on the individual clinical response.

Method of administration

Intravenous infusion or injection.

FibCLOT should be administered by slow intravenous infusion at maximum rate of 4 mL/min.

For instructions on reconstitution of the product before administration, see sections 6.2 and 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Thromboembolism

There is a risk of thrombosis when patients 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 peri- 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.

Allergic or anaphylactic-type reactions

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.

Transmissible agents

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV) and for the non-enveloped hepatitis A virus (HAV). The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (foetal infection) and for individuals with immunodeficiency or increased erythropoiesis (*e.g.* haemolytic anaemia).

Appropriate vaccination (hepatitis A and B) should be considered for patients in regular/repeated receipt of human plasma-derived fibrinogen.

Immunogenicity

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.

Sodium content

This medicinal product contains up to 69 mg sodium per vial, equivalent to 3.45% of the WHO recommended maximum daily intake of 2 g sodium for an adult. This should be taken into consideration in patients following a strict low sodium diet.

Paediatric population

Same warnings and precaution apply to the paediatric population.

4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Fertility, pregnancy and lactation

The safety of human plasma fibrinogen products for use in human pregnancy and during lactation 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 foetus or the neonate are to be expected.

4.7 Effects on ability to drive and use machines

FibCLOT has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Tabulated list of adverse reactions

The adverse reactions presented in the table below have been reported from data in 47 patients with congenital fibrinogen deficiency included in three clinical interventional studies and in one non-interventional post-marketing safety study. During these studies, 39 adverse reactions have been reported in 14/47 (29.8%) patients who received a total of 631 infusions of FibCLOT.

The most frequently reported reaction following FibCLOT administration was headache which occurred in 1.4% of infusions (9/631 infusions), all of them were mild to moderate in intensity, occurred within 48 hours following the infusion, and resolved without sequelae.

The adverse drug reactions are described according to the MedDRA classification (System Organ Class and Preferred Term Level). Frequencies have been estimated on a per-infusion basis according to the following conventions: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$).

Table 1: Adverse drug-reactions in paediatric and adult population in congenital deficiency

MedDRA Standard System Organ Class	Adverse reactions	Frequency per infusion
Immune system disorders	Allergic/anaphylactic-type reactions (including anaphylactic shock, pallor, vomiting, cough, blood pressure decreased, chills, urticaria)	Uncommon*
Nervous system disorders	Headache	Common

	Dizziness	Uncommon
Ear and labyrinth disorders	Tinnitus	Uncommon
Vascular disorders	Thromboembolic episodes (including deep vein thrombosis, superficial vein thrombosis) (see section 4.4)	Uncommon
Respiratory, thoracic and mediastinal disorders	Asthma	Uncommon
Gastrointestinal disorders	Vomiting**	Uncommon
Skin and subcutaneous tissue disorders	Rash erythematous	Uncommon
	Erythema	Uncommon
	Skin irritation	Uncommon
	Night sweats	Uncommon
General disorders and administration site conditions	Feeling hot	Uncommon

* in paediatric patients “common”

**vomiting associated to headache

For safety with respect to transmissible agents, see section 4.4.

The overall safety profile does not differ in patients treated with FibCLOT in other clinical situations requiring fibrinogen therapy.

Paediatric population:

Among the 47 patients included in the congenital fibrinogen deficiency safety analysis, 26 were <18 years including 5 between 12-17 years, 11 between 6-11 years and 10 ≤6 years. Frequency, type and severity of adverse reactions are similar in adult and paediatric patients except for allergic /anaphylactic type reactions that occurred with a common frequency (in 2 infants aged 1 and 5 year-old).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme, website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

In order to avoid overdosage, regular monitoring of the plasma level of fibrinogen therapy is indicated (see section 4.2).

In case of overdosage, the risk of development of thromboembolic complications is enhanced.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihæmorrhagics, human fibrinogen, ATC code: B02BB01

Human fibrinogen (coagulation factor I), in the presence of thrombin, activated coagulation factor XIII (FXIIIa) and calcium ions, is converted into a stable and elastic three-dimensional fibrin hæmostatic 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.

In congenital fibrinogen deficiency, 3 multicentre, open-label, non-randomised clinical studies (one in adults, one in adults, adolescents and children and one in children) evaluated the clinical pharmacology, safety and efficacy of FibCLOT. In addition, one non-interventional post-marketing safety study included adults and paediatric patients.

The clinical pharmacology study part of each clinical study (see section 5.2) enrolled a total of 31 patients with afibrinogenaemia who received a fixed single-dose of 0.06 g/kg of FibCLOT. A normalisation of global coagulation tests (*e.g.* activated partial thromboplastin time [aPTT] and prothrombin time [PT]) was achieved at fibrinogen levels at or above 0.5 g/L. Median change of maximum clot firmness (MCF) from pre-infusion to 1 hour post-infusion was 6.3 mm for patients <40 kg body weight and 10.0 mm for patients ≥40 kg body weight.

Adult population

Across all studies in congenital fibrinogen deficiency, 19 patients ≥18 years with a median age of 30 years (range 19-78 years) were enrolled for efficacy studies either for on-demand treatment bleeding or surgery, of which 18 were with afibrinogenaemia and 1 with a dysfibrinogenaemia. FibCLOT was administered for:

- 74 nonsurgical bleeding episodes in 12 patients (including 6 major episodes in 3 patients),
- 24 surgical procedures in 8 patients (including 8 major procedures in 5 patients).

The majority (94.9%) of the events (93/98) were resolved with a single dose of FibCLOT (0.050 g/kg for bleeding episodes and 0.055 g/kg for surgical procedure).

Paediatric population

Clinical efficacy analysis in interventional studies was based on 20 paediatric patients <18 years with afibrinogenaemia (aged 1 to 17) who received FibCLOT on 80 occasions either on-demand treatment of bleeding or prevention of excessive bleeding during surgery. Fourteen patients were treated with FibCLOT for 55 bleeding episodes and 15 patients for 25 surgical procedures. The median doses per infusion were 0.064 g/kg for bleeding episodes in a population with a mean body weight of 30 kg and 0.069 g/kg for surgical procedures in a population with a mean body weight of 26 kg. The majority (90.0%) of the events (72/80) were resolved with a single dose of FibCLOT.

In a post marketing study, 9 patients (including 4 children) have been treated for long term prophylaxis for at least 12 months with a median dose of 0.059 g/kg once a

week. Among them, 3 younger patients received higher doses (median of 0.082 g/kg in toddler and 0.075 g/kg in children between 2 and 5 years of age).

5.2 Pharmacokinetic properties

In plasma, the biological half-life of fibrinogen is 3-4 days.

The product is administered intravenously and is immediately available in the plasma at concentration corresponding to the dosage administered with almost complete recovery ranging from 79 to 110% (geometric mean of 93.6% (geometric CV 21%)) as reported in a clinical pharmacology study including 14 adult and adolescent patients with afibrinogenaemia.

A population pharmacokinetic model with allometric (body weight) scaling was developed using data collected in 31 patients with afibrinogenaemia aged 1 to 48 years: the parameters estimated are shown in Table 2. Children and adolescents <40 kg body weight had higher clearance, shorter half-life, and lower recovery at one hour post-infusion than adolescents and adults ≥40 kg. It can be expected that a body weight of <40 kg covers the age range from birth up to about 12 years old.

Table 2: Summary of FibCLOT pharmacokinetic parameters for activity data after infusion of 0.06 g/kg based on population PK parameters estimates and incremental recovery by body weight and age group: Geometric mean (geometric CV (%))

	Patients <40 kg	Patients ≥ 40 kg	Children ≤6 years	Children 7 to 12 years	Adolescents 13 to <18 years	Adults ≥18 years
Number of patients	12	19	6	8	3	14
AUC _{0-∞} (g.h/L)	81 (23)	133 (26)	74 (15)	93 (23)	144 (30)	136 (26)
Cl (mL/h/kg)	0.74 (23)	0.45 (25)	0.81 (15)	0.65 (23)	0.43 (27)	0.44 (25)
t _{1/2} (h)	49.0 (12)	66.7 (19)	46.6 (10)	52.1 (10)	64.2 (10)	69.3 (20)
MRT (h)	70.7 (12)	96.2 (13)	67.3 (10)	75.2 (10)	92.6 (10)	100.0 (20)
V _{ss} (mL/kg)	52.2 (16)	43.2 (17)	54.4 (10)	48.6 (19)	39.5 (19)	43.8 (18)
Fibrinogen concentration at 1 hour (g/L)	1.15 (20)	1.40 (22)	1.12 (14)	1.21 (24)	1.56 (27)	1.38 (23)
Incremental recovery at 1 hour (g/L per g/kg)	19.1 (20)	23.3 (21)	18.7 (14)	20.1 (24)	25.4 (24)	23.1 (22)

AUC_{0-∞}: Area under the curve from 0 to infinity, Cl: clearance, t_{1/2}: terminal elimination half-life, MRT: Mean residence time, V_{ss}: volume of distribution at steady state

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity as well as thrombogenicity.

Given the nature of the product carcinogenicity studies were not conducted. Animal reproduction studies have not been performed since fibrinogen is a normal constituent of the human body.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

<u>Powder:</u>	Arginine hydrochloride
	Isoleucine
	Lysine hydrochloride
	Glycine
	Sodium citrate dihydrate
<u>Solvent:</u>	Water for injections.

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products and should be administered by a separate injection/infusion line.

6.3 Shelf life

3 years.

Chemical and physical in-use stability has been demonstrated for 24 hours at 25 °C. The product, after reconstitution, should be used immediately and not stored.

6.4 Special precautions for storage

Do not store above 25°C.

Do not freeze.

Store in the original outer package in order to protect from light and moisture.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

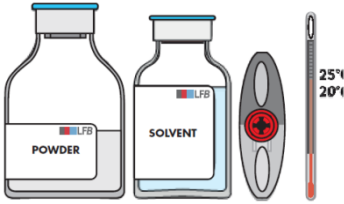
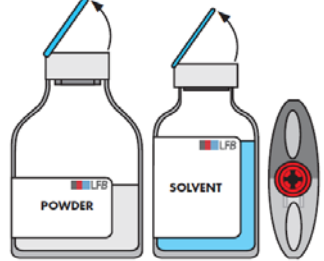
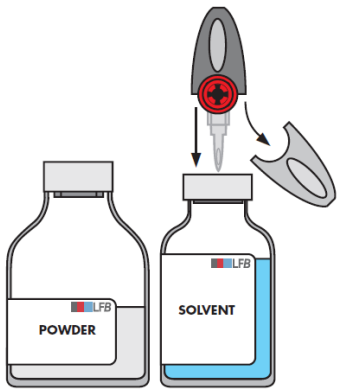
One pack contains:

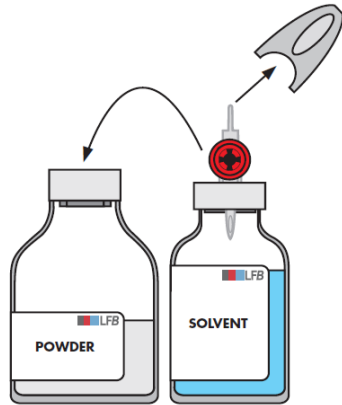
- Powder (1.5 g human fibrinogen) in a colourless type I glass vial sealed with a siliconised bromobutyl stopper, an aluminium cap and a plastic disc.
- Solvent (100 mL water for injections) in a type II glass vial sealed with a bromobutyl stopper, an aluminium cap and a plastic disc.
- Transfer system equipped with a sterile filtering air vent.
- Infusion set equipped with 15 µm filter.

6.6 Special precautions for disposal

Reconstitution:

Use current guidelines for aseptic procedure.

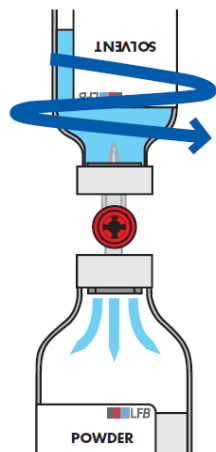
	If necessary, increase the temperature of the two vials (powder and solvent) to ambient temperature.
	Remove the protective cap from the solvent vial and from the powder vial. Disinfect the surface of each stopper.
	Remove the translucent protective sheath from the transfer system and completely insert the exposed piercing spike through the centre of the stopper of the solvent vial while simultaneously twisting the piercing spike.



Remove the second grey protective sheath from the other end of the transfer system.

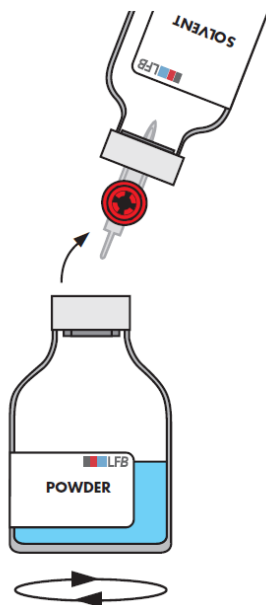
Turn the solvent vial and quickly push the free end of the piercing spike into the center of the stopper of the powder vial to allow the solvent to transfer into the powder.

Ensure that the spike always remains immersed in the solvent to avoid releasing the vacuum prematurely.



During transfer, direct the jet of solvent over the entire surface of the powder and along the wall of the vial by a rotational horizontal movement. Ensure that all of the solvent is transferred.

The vacuum is automatically released at the end of the transfer procedure by sterile air through the venting part of the transfer system.



Remove the empty vial (solvent) with the transfer system.

Gently swirl for a few minutes with a rotating movement to avoid the formation of foam until the powder has completely dissolved.

The reconstituted product should be examined visually prior to administration in order to ensure that it does not contain particulate matter. The reconstituted solution should be almost colourless, slightly opalescent. Do not use solutions which are cloudy or contain deposits.

Administration:

FibCLOT should only be administered intravenously, as a single dose, immediately after reconstitution, at no more than 4 mL/min.

The use of an infusion set equipped with a 15 µm filter, as the one supplied within the packaging, is mandatory.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05/01/2023

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