SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Fibrogammin 250/1250 IU
Powder and solvent for solution for injection or infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Active substance: Fibrogammin is a purified concentrate of blood coagulation factor XIII (FXIII). It is derived from human plasma and is presented as a white powder.

Each vial contains nominally 250 or 1250 IU human plasma coagulation factor XIII.

Fibrogammin contains approximately 62.5 IU/ml (250 IU/4 ml or 1250/20 ml) of human plasma coagulation factor XIII when reconstituted with 4 ml or 20 ml water for injections, respectively.

The specific activity of Fibrogammin is approximately 3.1 – 13.3 IU/mg protein.

Excipients with known effect:
Sodium (as chloride and hydroxide): 2.78 to 4.36 mg/ml (120 to 189 mmol/L)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection/infusion.
White powder and clear, colourless solvent.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Fibrogammin is indicated for adult and paediatric patients.

Congenital deficiency of Factor XIII and resultant haemorrhagic diathesis, haemorrhages and disturbances in wound healing.

4.2 Posology and method of administration

Posology
1 ml is equivalent to 62.5 IU, and 100 IU are equivalent to 1.6 ml, respectively.

Important: The amount to be administered and the frequency of administration should always be orientated towards clinical efficacy in the individual case.

Dosage
The dosing regimen should be individualised based on body weight, laboratory values, and the patient's clinical condition.

Routine prophylaxis dosing schedule for treatment of congenital FXIII deficiency
Initial dose

- 40 International Units (IU) per kg body weight
- The injection rate should not exceed 4 ml per minute.

Subsequent dosing

- Dosing should be guided by the most recent trough FXIII activity level, with dosing every 28 days (4 weeks) to maintain a trough FXIII activity level of approximately 5 to 20%.
- Recommended dosing adjustments of ± 5 IU per kg should be based on trough FXIII activity levels as shown in Table 1 and the patient's clinical condition.
- Dosing adjustments should be made on the basis of a specific, sensitive assay used to determine FXIII levels.

An example of dose adjustment using the standard Berichrom® FXIII activity assay is outlined in Table 1 below.

Table 1: Dose adjustment using the Berichrom® FXIII activity assay

Factor XIII Activity Trough Level (%)	Dosage Change
One trough level of <5%	Increase by 5 units per kg
Trough level of 5% to 20%	No change
Two trough levels of >20%	Decrease by 5 units per kg
One trough level of >25%	Decrease by 5 units per kg

The potency expressed in units is determined using the Berichrom® FXIII activity assay, referenced to the current International Standard for Blood Coagulation Factor XIII, Plasma. Therefore, a unit is equivalent to an International Unit.

Prophylaxis prior to surgery
After the patient's last routine prophylactic dose, if a surgery is scheduled:

- Between 21 and 28 days later – administer the patient's full prophylaxis dose immediately prior to surgery and the next prophylactic dose should be given 28 days later.

- Between 8 and 21 days later – an additional dose (full or partial) may be administered prior to surgery. The dose should be guided by the patient's FXIII activity levels and clinical condition and should be adjusted according to the half-life of Fibrogammin.
- Within 7 days of last dose – additional dosing may not be needed.

Adjustments to dosing may be different from these recommendations and should be individualised, based on FXIII activity levels and the patient's clinical condition. All patients should be monitored closely during and after surgery.

It is recommended to monitor the increase in FXIII-activity with a FXIII assay. In the case of major surgery and severe haemorrhage, the aim is to obtain values within the normal range for healthy people, i.e. 0.7 -1.4 IU/ml.

Paediatric population
The posology and method of administration in children and adolescents is based on body weight and is therefore generally based on the same guidelines as for adults. The dose and/or frequency of administration for each individual should always be guided by the clinical effectiveness and FXIII activity levels. (Please also refer to sections 5.1 and 5.2.)

Elderly population
The posology and method of administration in elderly people (> 65 years) has not been established in clinical studies.

Method of administration
For instructions on reconstitution of the medicinal product before administration, see section 6.6.
After reconstitution the solution should be clear or slightly opalescent. The preparation should be warmed to room or body temperature before administration. Slowly inject or infuse intravenously at a rate which the patient finds comfortable. The injection or infusion rate should not exceed approximately 4ml per minute.

Observe the patient for any immediate reaction. If any reaction takes place that might be related to the administration of Fibrogammin, the rate of infusion should be decreased or the infusion stopped, as required by the clinical condition of the patient.

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

In patients with known allergies to the product, with symptoms such as generalised urticaria, rash, a fall in blood pressure, dyspnoea, antihistamines and corticosteroids may be administered prophylactically.

Allergic-type hypersensitivity reactions are possible with Fibrogammin. If symptoms of hypersensitivity (such as hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis) occur, the Fibrogammin infusion should be discontinued immediately. In case of shock, the current medical standards for shock treatment should be implemented.

In cases of fresh thromboses caution should be exercised on account of the fibrin-stabilising effect of Factor XIII.

Immunogenicity
Development of inhibitory antibodies against FXIII has been detected in patients receiving Fibrogammin. Therefore, patients should be monitored for possible development of inhibitory antibodies. The presence of inhibitory antibodies may manifest as an inadequate response to treatment. If expected plasma FXIII activity levels are not attained, or if breakthrough bleeding occurs during prophylaxis, FXIII inhibitory antibody concentrations should be measured.

Note for diabetic patients
Fibrogammin contains glucose (24 mg per 250 IU). When administering a dose of 40 IU/kg body weight to a patient with 75 kg body weight, a maximum of 288 mg glucose will be supplied.
Note for patients on a low sodium diet
Fibrogammin contains 124.4 to 195.4 mg (5.41 to 8.50 mmol) sodium per dose (40 IU/body weight – for average of 70 kg), if the recommended dose (2800 IU = 44.8 ml) is applied. To be taken into consideration in patients on a controlled sodium diet.
Virus safety
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 viruses hepatitis A and parvovirus B19.

It is strongly recommended that whenever Fibrogammin is administered to a patient, the product name and batch number are recorded in order to maintain a link between the patient and the batch of the product.

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

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Pregnancy
Limited data on the clinical use of Fibrogammin in pregnancy did not show any negative effects on the course of gestation and the peri- or postnatal development. The use of Fibrogammin may be considered during pregnancy, if necessary.

Breastfeeding
There are no data on the excretion of Fibrogammin into human milk. However, based on its large molecular size excretion into milk is unlikely and due to its proteinaceous character, absorption of intact molecules by the infant is also unlikely. Therefore, Fibrogammin can be used during breastfeeding.

Fertility
There are no data regarding effects of Fibrogammin on fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

The following adverse reactions are based on post-marketing experience.

Tabulated list of adverse reactions
The table presented below is according to the MedDRA system organ classification. Frequencies have been evaluated according to the following convention:
very common: ≥ 1/10, common: ≥ 1/100 and < 1/10, uncommon: ≥ 1/1,000 and < 1/100, rare: ≥ 1/10,000 and < 1/1,000, very rare: < 1/10,000.

MedDRA Standard System Organ Class	**Adverse Reaction**	**Frequency**
Immune System Disorders	Allergoid-anaphylactoid reactions (like generalised urticaria, rash, fall in blood pressure, dyspnoea)	Rare
	Development of inhibitors to FXIII	Very rare

General Disorders and Administration Site Conditions	Rise in temperature	Rare

If allergoid-anaphylactoid reactions occur, the administration of Fibrogammin has to be discontinued immediately and an appropriate treatment initiated. The current medical standards for shock treatment are to be observed.

Paediatric population
The safety profile for paediatric patients is no different from that of adults in clinical studies.

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

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 the UK 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

No cases of overdose have been reported.

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihaemorrhagics
ATC code: B02B D07

Biochemically, factor XIII acts as transglutaminase.
Factor XIII connects the amino group of lysine with glutamine via its enzymatic function (transamidase activity), thereby leading to the cross-linking of fibrin molecules. This is the final stage of blood coagulation. Fibrin cross-linking and stabilisation promote the penetration of fibroblasts and support wound healing.

Paediatric population
In clinical studies that included subjects with congenital FXIII deficiency <18 years old, the prophylactic administration with Fibrogammin every 28 days was successful in maintaining trough FXIII activity levels of approximately 5% to 20%.

5.2 Pharmacokinetic properties

Distribution
The product is administered intravenously, and is thus immediately bioavailable resulting in a plasma concentration corresponding to the applied dose.

Elimination
In patients with congenital factor-XIII-deficiency the biological half-life of Fibrogammin was determined to be 6.6 ± 2.29 days (mean ± SD).
Fibrogammin is metabolised in the same way as is the endogenous coagulation factor XIII.

An overview of pharmacokinetic parameters (adult population/18 years and older) is given in the following table:

Parameters	**Median (min-max)**
AUC_{ss} 0 - ∞ (units/hr/ml)	182.9 (133.5-300.2)
$C_{ss\ max}$ (units/ml)*	0.9 (0.6-1.2)
$C_{ss\ min}$ (units/ml)*	0.07 (0.0-0.16)
T_{max} (hr)	1.2 (0.7-4.2)
T½ [days]	7.8 (3.1-11.02)
CL [ml/hr/kg]	0.22 (0.13-0.30)
V_{ss} [ml/kg]	49.4 (31.65-62.91)
MRT [days]	11.7 (5.7-17.02)

AUCss (0-∞): Area under the plasma concentration curve from time 0 to infinity at steady state
*100% activity corresponds to 1 unit/ml
Css max: Peak concentration at steady state
Css min: Trough concentration at steady state
T_{max}: Time to peak concentration
T½: Half-life
CL: Clearance
Vss: Volume of distribution at steady state
MRT: Mean residence time

Paediatric population
Of the 188 unique subjects in the Factor XIII concentrate (human) clinical studies, 117 were subjects < 18 years of age at the time of enrolment (1 month to <2 years, n= 17; 2 to <12 years, n=62; 12 to <16 years, n=30; 17 to 18 years, n=8). In the pharmacokinetic study PK 2002, 5 of the 14 subjects ranged in age from 2 to < 18 years (2-11 years, n=3; 12-16 years, n=2; 17-18 years, n=0). Subjects less than 16 years had a shorter half-life and faster clearance (half-life: 5.7±1.00 days; clearance: 0.291±0.12 ml/hr/kg) compared to adults (half-life: 7.1 ± 2.74 days, clearance: 0.22 ± 0.07 ml/hr/kg).

The product has a shorter half-life and faster clearance in children compared to adults. However, since across all age groups dosing is individually determined by subject weight and adjusted by trough FXIII activity, no specific age related dosing is needed.

5.3 Preclinical safety data

The proteins contained in Fibrogammin are sourced from human plasma and act like human plasma proteins.

Single and repeated dose toxicity studies in animals did not reveal a toxic potential for Fibrogammin.

Studies on reproduction and embryo-foetal development have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Human albumin
Glucose monohydrate
Sodium chloride*
Sodium hydroxide (for pH adjustment)
*see also section 4.4

Solvent:
Water for Injections

6.2 Incompatibilities

Fibrogammin must not be mixed with other medicinal products, diluents, or solvents except those mentioned in section 6.6 and should be administered by a separate infusion line.

6.3 Shelf life

3 years

Do not use after the expiry date given on the pack and container.

Do not freeze reconstituted solution.
Chemical and physical in-use stability has been demonstrated for 24 hours at 25°C.
From a microbiological point of view, unless the method of opening and reconstitution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (+2 to +8 °C).
Do not freeze.

Keep the vial in the outer carton in order to protect from light.
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Vials:
250 IU
Powder: injection vial of colourless glass, sealed with a bromobutyl rubber stopper, aluminium cap and plastic disc.
Solvent (Water for Injections): vial of colourless glass

1250 IU
Powder: injection vial of colourless glass, sealed with a bromobutyl rubber stopper, aluminium cap and plastic disc.
Solvent (Water for Injections): vial of colourless glass.

Presentations:
Pack with 250 IU
1 vial with powder
1 vial with 4 ml Water for Injections
1 filter transfer device 20/20 (Mix2Vial)
Administration set (inner box):
1 disposable 5 ml syringe
1 venipuncture set
2 alcohol swabs
1 non-sterile plaster

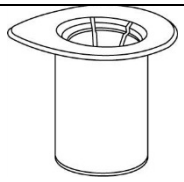
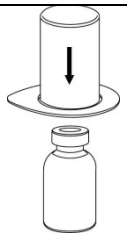
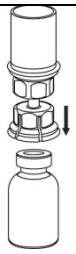
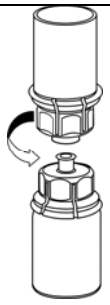
Pack with 1250 IU
1 vial with powder
1 vial with 20 ml Water for Injections
1 filter transfer device 20/20 (Mix2Vial)
Administration set (inner box):
1 disposable 20 ml syringe
1 venipuncture set
2 alcohol swabs
1 non-sterile plaster

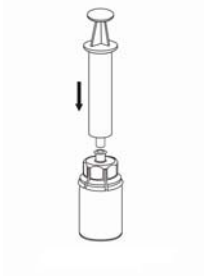
6.6 Special precautions for disposal

General instructions

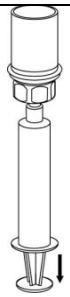
- The solution should be clear or slightly opalescent. After filtering/withdrawal (see below) the reconstituted product should be inspected visually for particulate matter and discoloration prior to administration.
- Reconstitution and withdrawal must be carried out under aseptic conditions.
- Do not use solutions which are cloudy or contain residues (deposits/particles).

Reconstitution:
Bring the solvent to room temperature. Ensure product and solvent vial flip caps are removed and the stoppers are treated with an antiseptic solution and allowed to dry prior to opening the Mix2Vial package.

 1	1. Open the Mix2Vial package by peeling off the lid. Do **not** remove the Mix2Vial from the blister package!
 2	2. Place the **solvent vial** on an even, clean surface and hold the vial tight. Take the Mix2Vial together with the blister package and push the spike of the **blue** adapter end **straight down** through the solvent vial stopper.
 3	3. Carefully remove the blister package from the Mix2Vial set by holding at the rim, and pulling **vertically** upwards. Make sure that you only pull away the blister package and not the Mix2Vial set.
 4	4. Place the **product vial** on an even and firm surface. Invert the solvent vial with the Mix2Vial set attached and push the spike of the **transparent** adapter end **straight down** through the product vial stopper. The solvent will automatically flow into the product vial.
 5	5. With one hand grasp the product-side of the Mix2Vial set and with the other hand grasp the solvent-side and unscrew the set counter-clockwise carefully into two pieces. Discard the solvent vial with the blue Mix2Vial adapter attached.
 6	6. Gently swirl the product vial with the transparent adapter attached until the substance is fully dissolved. Do not shake.

 7	7. Draw air into an empty, sterile syringe. While the product vial is upright, connect the syringe to the Mix2Vial's Luer Lock fitting by screwing clockwise. Inject air into the product vial.

Withdrawal and application

 8	8. While keeping the syringe plunger pressed, turn the system upside down and draw the solution into the syringe by pulling the plunger back slowly.
 9	9. Now that the solution has been transferred into the syringe, firmly hold on to the barrel of the syringe (keeping the syringe plunger facing down) and disconnect the transparent Mix2Vial adapter from the syringe by unscrewing counter-clockwise.

Care should be taken that no blood enters the syringe filled with product, as there is a risk that the blood could coagulate in the syringe and fibrin clots could therefore be administered to the patient.

In case more than one vial of Fibrogammin is required, it is possible to pool several vials of Fibrogammin for a single infusion via a commercially available infusion device.

The Fibrogammin solution must not be diluted.

The reconstituted solution should be administered by a separate injection / infusion line by slow intravenous injection, at a rate not exceeding 4 ml per minute.

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

7 MARKETING AUTHORISATION HOLDER

CSL Behring GmbH

Emil-von-Behring-Strasse 76
35041 Marburg
Germany

8 MARKETING AUTHORISATION NUMBER(S)

PL 15036/0006

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

22 June 1998 / 30 October 2003

10 DATE OF REVISION OF THE TEXT

20/07/2018