

COMPANY CORE DATA SHEET – CCDS (EDS/CORE/ENGLISH)

FIBROGAMMIN[®] 250/1250

Rev.: **08-OCT-2014** / Changes based on new clinical data / stability after reconstitution

Supersedes previous versions

Rev.: 15-MAY-2013 / Introduction Mix2Vial / adaptation to QRD

Rev.: 19-JUN-2012 / Virus filtration / editorial changes

1. NAME OF THE MEDICINAL PRODUCT

Fibrogammin® 250/1250

Powder and solvent for solution for injection/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, 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 and 1250 IU/20 ml) of human plasma coagulation factor XIII when reconstituted with 4 and 20 ml water for injection, respectively.

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

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

- for prophylactic treatment of congenital FXIII deficiency and
- for peri-operative management of surgical bleeding with congenital FXIII deficiency.

Fibrogammin is furthermore indicated

- for haemorrhagic diatheses caused completely or in part by acquired FXIII deficiency
- for supportive therapy in case of disturbance in wound healing, especially in ulcer cruris, after large surgery or injuries.

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 oriented towards the clinical efficacy in the individual case.

Dosage

The dosing regimen should be individualized 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 than these recommendations and should be individualized based on FXIII activity levels and the patient's clinical condition. All patients should be monitored closely during and after surgery.

Thus, it is recommended to monitor the increase in FXIII-activity with a FXIII-assay. In the case of major surgery and severe haemorrhages the aim is to obtain near normal values (healthy persons: 70% - 140%).

Acquired Factor-XIII-deficiency

For treatment of haemorrhagic diatheses at least 15-20 International Units (IU) per kg body weight daily should be administered until symptoms improve and normal FXIII levels are achieved spontaneously, respectively.

Supportive therapy in disorder of wound healing

10 International Units (IU) per kg body weight on the day of operation and once-daily on the following 3 days. In high-risk patients the individual dose can be increased to 15-20 IU/kg b.w.

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 documented in clinical studies.

Method of administration

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

In patients with known allergies to the product (with symptoms like generalised urticaria, rash, 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 observed.

In cases of fresh thromboses caution should be exercised due to the fibrin-stabilizing effect of FXIII.

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 while receiving prophylaxis, FXIII inhibitory antibody concentrations should be measured.

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 viruses.

It is strongly recommended that every time that Fibrogammin 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.

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

4.5 Interactions with other medicinal products and other forms of interactions

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 ($\geq 1/10$); 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 ($< 1/10,000$).

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 not 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.

[For EU only: Please insert the national reporting system according to Appendix V QRD template]

4.9 Overdose

No cases of overdose have been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihaemorrhagics
ATC code: B02B D07

Factor XIII connects the amino group of lysine with glutamine by the use of its enzymatical function (transamidase activity) thereby leading to the cross-linking of fibrin molecules. Fibrin cross-linking and stabilization 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 \pm SD). Fibrogammin is metabolized in the same way as is the endogenous coagulation factor XIII.

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

Parameters	Median (min-max)
AUC ss, 0-inf (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)
Half-life [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)

AUC ss, (0-inf) = Area under the plasma concentration curve from time 0 to infinity at steady state

* 100% activity corresponds to 1 unit/ml

C_{ss, max}: Peak concentration at steady state

C_{ss, min}: Trough concentration at steady state

T_{max}: Time to peak concentration

CL: Clearance

V_{ss}: 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 dose and repeated dose toxicity studies in animals did not reveal a toxic potential for Fibrogammin.

Studies on reproduction and embryofoetal development were not performed.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:

Human albumin

Glucose monohydrate

Sodium chloride

NaOH (for pH adjustment)

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.

Chemical and physical in-use stability has been demonstrated for 24 hours at ≤ 25 °C. From a microbiological point of view, the product should be used immediately. If not administered immediately, storage shall not exceed 4 hours at room temperature. Do not refrigerate or freeze the reconstituted solution.

6.4 Special precautions for storage

Store in a refrigerator (+2 °C 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 rubber stopper (bromobutyl rubber), an aluminium cap and a plastic disc.

Solvent (water for injections): vial of colourless glass.

1250 IU

Powder: injection vial of colourless glass, sealed with a rubber stopper (bromobutyl rubber), an aluminium cap and a plastic disc.

Solvent (water for injections): injection 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)

Pack with 1250 IU

1 vial with powder

1 vial with 20 ml water for injections

1 filter transfer device 20/20 (Mix2Vial)

Not all pack sizes may be marketed.

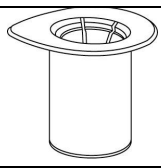
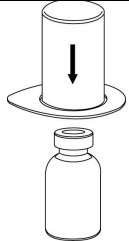
6.6 Special precautions for disposal and other handling


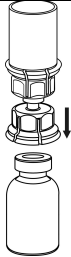
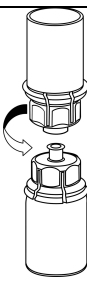

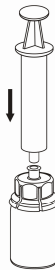
General instructions

- 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).

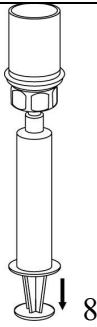
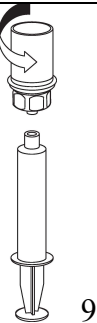
Reconstitution

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. Open the Mix2Vial package by peeling off the lid. Do not remove the Mix2Vial from the blister package!
	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.

 <p>3</p>	<p>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.</p>
 <p>4</p>	<p>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.</p>
 <p>5</p>	<p>5. With one hand grasp the product-side of the Mix2Vial set and with the other hand grasp the solvent-side and unscrew counterclockwise the set carefully into two pieces. Discard the solvent vial with the blue Mix2Vial adapter attached.</p>
 <p>6</p>	<p>6. Gently swirl the product vial with the transparent adapter attached until the substance is fully dissolved. Do not shake.</p>
 <p>7</p>	<p>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.</p>

Withdrawal and application

	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. 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 counterclockwise.

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-Str. 76
35041 Marburg
Germany

8. MARKETING AUTHORISATION NUMBER(S)

– country specific –

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

– country specific –

10. DATE OF REVISION OF THE TEXT

October 2014