SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

FIBRYGA 1g. Powder and solvent for solution for injection / infusion.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Human Fibrinogen

Each bottle of FIBRYGA contains 1 g human fibrinogen. After reconstitution with 50 ml water for injections FIBRYGA contains approximately 20 mg/ml human fibrinogen.

The content of clottable protein is determined according to the European Pharmacopoeia for human fibrinogen.

Produced from the plasma of human donors.

Excipients with known effect: sodium up to 132 mg (5.8 mmol) per bottle.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection / infusion.

The powder is white or pale yellow, and hygroscopic, also appearing as friable solid.

The solvent is a clear and colorless liquid.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

As complementary therapy to management of uncontrolled severe haemorrhage in patients with acquired hypofibrinogenaemia in the course of surgical intervention.

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. 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- 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 secured and above 0.5 g/l until wound healing is complete.

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

$$\text{Dose (mg/kg body weight)} = \frac{[\text{Target level (g/L)} - \text{measured level (g/L)}]}{0.018 \text{ (g/L per mg/kg body weight)}}$$

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

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.

Posology in specific populations

Paediatric Patients

Currently available data are described in section 4.8 and 5.1 but no recommendation on a posology can be made in children.

Elderly patients

Clinical studies of FIBRYGA did not include patients aged 65 years and over to provide conclusive evidence as to whether or not they respond differently than younger patients.

2. Treatment of bleeding

Bleeding in patients with congenital hypo- or afibrinogenaemia

Bleeding should be treated to achieve a recommended target fibrinogen plasma level of 1 g/l. This level should be maintained until haemostasis is secured.

Bleeding in patients with acquired fibrinogen deficiency

The recommended initial dose for patients with uncontrolled severe bleeding in the course of

surgical intervention is 4 g. Additional doses of 4 g are to be administered as needed to bleeding patients when FIBTEM A20 is ≤12 mm (or equivalent values generated by other thromboelastometry/thrombelastography methods). Monitor the patient's fibrinogen plasma level or the clot firmness of the fibrin-based clot during treatment with FIBRYGA.

Posology in specific populations

Paediatric Patients

There are no data available from clinical studies in this age group. No recommendation on a posology for the treatment of bleeding in acquired fibrinogen deficiency can be made in children.

Elderly patients

Clinical studies of FIBRYGA did not include sufficient numbers of patients aged 65 years and over to provide conclusive evidence as to whether or not they respond differently than younger patients.

Method of administration

Intravenous infusion or injection.

FIBRYGA should be administered slowly intravenously at a recommended maximum rate of 5 mL per minute for patients with congenital hypo- or afibrinogenaemia and at a recommended maximum rate of 10 mL per minute for patients with acquired fibrinogen deficiency.

For instructions 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

Thromboembolism

There is a risk of thrombosis when patients, with either congenital or acquired 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 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.

Acquired hypofibrinogenaemia is associated with low plasma concentrations of all coagulation factors (not only fibrinogen) and inhibitors and so treatment with blood products containing coagulation factors should be considered. Careful monitoring of the coagulation system is necessary.

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.

Sodium Level

FIBRYGA contains up to 132 mg (5.8 mmol) sodium per bottle, equivalent to 6.6% of the WHO recommended maximum daily intake of 2 g sodium for an adult. To be taken into consideration by 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, other pathogens and theoretically to Creutzfeldt - Jakob disease (CJD).

The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV, and for the non-enveloped 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 (fetal 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 products.

It is strongly recommended that every time that FIBRYGA 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.

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 concentrate.

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

Pregnancy

Animal reproduction studies have not been conducted with FIBRYGA (see section 5.3). 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 FIBRYGA 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 FIBRYGA is excreted in human milk. The use of FIBRYGA in lactating women has not been investigated in clinical trials.

Fertility

There are no data on fertility available.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

There are no robust data on the frequency of adverse reactions from clinical trials with this product.

In clinical studies, the following adverse reactions have been reported: mild pyrexia, reported from one patient, and drug eruption, in form of mild skin reaction of itchiness and redness after product administration, also reported from one patient.

The following adverse reactions have been reported for FIBRYGA and other fibrinogen concentrates:

MedDRA Standard System Organ Class	Undesirable effects	Frequency
Immune system disorders:	Allergic or anaphylactic-type reactions Skin reactions	Unknown
Vascular disorders:	Thromboembolic episodes (including myocardial infarction and pulmonary embolism) (see section 4.4) Thrombophlebitis	Unknown
General disorders and administration site conditions:	Increase in body temperature (pyrexia)	Unknown

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

Paediatric population:

The 8 patients included in the congenital fibrinogen deficiency safety analysis were 12 to 18 years of age.

The overall safety profile does not differ between adults and adolescents.

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.

4.9 Overdose

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihaemorrhagics, 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 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.

An open-label, prospective, randomized, controlled, two-arm cross-over single-dose pharmacokinetic phase II study in 22 patients with congenital fibrinogen deficiency (afibrinogenemia) (see section 5.2) also evaluated the maximum clot firmness (MCF) as a surrogate marker for haemostatic efficacy (FORMA-01). MCF was determined by thromboelastometry (ROTEM) testing. For each patient, MCF was determined before (baseline) and one hour after the single-dose administration of FIBRYGA. MCF values were significantly higher after administration of FIBRYGA than at baseline (see the table below).

Table 1: Maximum clot firmness MCF [mm] (ITT population) n=22

Time point	Mean ± SD	Median (range)
Pre-infusion	0 ± 0	0 (0-0)
1 hour post-infusion	9.7± 3.0	10.0 (4.0-16.0)
Mean change (primary analysis)*	9.7 ± 3.0	10.0 (4.0-16.0)

MCF = maximum clot firmness; ITT = intention-to-treat.
*$p < 0.0001$ (95% confidence interval 8.37; 10.99)

An interim analysis of an ongoing prospective, open label, uncontrolled, multicentre phase III study (FORMA-02) was conducted in 13 patients with congenital fibrinogen deficiency (afibrinogenemia and hypofibrinogenemia), ranging in age from 13 to 53 years (2 adolescents, 11 adults). This included the treatment of 23 bleeding episodes and 4 surgical procedures. There was significant change from baseline in the MCF as measured by ROTEM and fibrinogen plasma levels. All of the treated bleeding episodes and surgical procedures studied were rated as successful (rating of good or excellent efficacy) by the investigator and by an independent adjudication committee using an objective scoring system.

The prospective, randomised, controlled study FORMA-05 investigated the haemostatic efficacy and safety of FIBRYGA by comparison with cryoprecipitate as fibrinogen supplementation sources in patients developing acquired fibrinogen deficiency during cytoreductive surgery for the extensive abdominal malignancy pseudomyxoma peritonei. The study included 43 adult patients in the Per Protocol (PP) analysis set, 21 patients treated with FIBRYGA and 22 patients treated with cryoprecipitate. Intraoperative fibrinogen supplementation was performed pre-emptively (i.e. after 60-90 minutes in surgery, when excessive blood loss was observed, but before 2 litres of blood had been lost) with doses of 4 g of FIBRYGA or of 2 pools of 5 units of cryoprecipitate, repeated as needed. During the 7.8 ± 1.7 hours of surgery, 6.5 ± 3 grams of FIBRYGA (89 ± 39 mg/kg bw) and 4.1 ± 2.2 pools of 5 units of cryoprecipitate were used, respectively. A median of 1 unit and 0.5 units RBC were administered intraoperatively to the patients treated with FIBRYGA and cryoprecipitate, respectively, with a median of 0 units RBC during the first 24 hours postoperatively in both groups (see the table below). No fresh frozen plasma or platelet concentrates were transfused during the study Haemostatic therapy based on fibrinogen supplementation was rated as successful for 100% of the surgeries in both groups by an independent adjudication committee using an objective scoring system.

Table 2: RBC* transfusion [units] intraoperatively and during the first 24 hours postoperatively (PP population)

Time frame	FIBRYGA group (n=21) Median (range)	Cryoprecipitate group (n=22) Median (range)
Intraoperatively	1 (0-4)	0.5 (0-5)
First 24 hours postoperatively	0 (0-2)	0 (0-2)

RBC = red blood cell concentrates; PP = per protocol.
*no transfusion of other allogeneic blood products, such as fresh frozen plasma or platelet concentrates, occurred

Paediatric population
FIBRYGA was administered in two clinical studies in 8 patients from 12 to 18 years of age(see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Human fibrinogen is a normal constituent of human plasma and acts like endogenous fibrinogen. In plasma, the biological half-life of fibrinogen is 3–4 days. FIBRYGA is administered intravenously and is immediately available in a plasma concentration corresponding to the dosage administered.
An open-label, prospective, randomized, controlled, two-arm cross-over phase II study in 22 patients with congenital fibrinogen deficiency (afibrinogenemia), ranging in age from 12 to 53 years (6 adolescents, 16 adults), compared the single-dose pharmacokinetic properties of FIBRYGA with those of another commercially available fibrinogen concentrate in the same patients (FORMA-01). Each patient received a single intravenous 70 mg/kg dose of FIBRYGA and the comparator product. Blood samples were drawn to determine the fibrinogen activity at baseline and up to 14 days after the infusion. The pharmacokinetic parameters of FIBRYGA in the per protocol (PP) analysis (n=21) are summarized in the table below.

Table 2: Pharmacokinetic Parameters (n=21) for Fibrinogen Activity (PP population*)

Parameter	Mean ± SD	Range
Half-life [hr]	75.9 ± 23.8	40.0–157.0
C_{max} [mg/dL]	139.0 ± 36.9	83.0–216.0
AUC_{norm} for dose of 70 mg/kg [mg*hr/mL]	113.7 ± 31.5	59.7–175.5
Clearance [mL/hr/kg]	0.67 ± 0.2	0.4–1.2
Mean residence time [hr]	106.3 ± 30.9	58.7–205.5
Volume of distribution at steady state [mL/kg]	70.2 ± 29.9	36.9–149.1

*One patient excluded from the PP population because of receiving <90% of the planned dose of FIBRYGA and Comparator product
C_{max} = maximum plasma concentration; AUC_{norm} = area under the curve normalised to the dose administered; SD = standard deviation

The incremental in vivo recovery (IVR) was determined from levels obtained up to 4 hours post-infusion. The median incremental IVR was 1.8 mg/dL (range, 1.08–2.62 mg/dL) increase per mg/kg. The median IVR indicates that a dose of 70 mg/kg will increase the patient's fibrinogen plasma concentration by approximately 125 mg/dL.

Pharmacokinetics in specific populations

No statistically relevant difference in fibrinogen activity was observed between male and female study participants. In the PP analysis, a small difference was seen in the half-life for patients less than 18 years of age (n=5), being 72.8 ± 16.5 hours as compared to 76.9 ± 26.1 hours for the adult group (n=16). Clearance was almost identical in both age groups, i.e., 0.68 ± 0.18 mL/hr/kg and 0.66 ± 0.21 mL/hr/kg, respectively.

Paediatric population

No pharmacokinetic data are available in paediatric patients <12 years of age.

5.3 Preclinical safety data

The safety of FIBRYGA has been demonstrated in several non-clinical safety pharmacology (cardiovascular effects, thrombogenic potential) and toxicology studies (acute toxicity, local tolerance). The non-clinical data reveal no special hazard for humans based on these studies. In the venous stasis test (Wessler test) FIBRYGA proved to be non-thrombogenic at doses up to 400 mg/kg body weight.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

L-arginine hydrochloride

Glycine

Sodium chloride

Sodium citrate dihydrate

Solvent

Water for Injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

30 months.

The chemical and physical in-use stability of the reconstituted solution has been demonstrated for 24 hours at room temperature (max. 30°C). From a microbiological point of view the product should be used immediately after reconstitution. If not used immediately, in-use storage times and conditions are the responsibility of the user. The reconstituted solution must not be frozen or stored in a refrigerator. Partially used bottles should be discarded.

6.4 Special precautions for storage

Do not store above 30°C. Do not freeze. Keep the bottle in the outer carton to protect from light.

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

6.5 Nature and contents of container

Each pack contains:

- 1 g human fibrinogen in a 100 ml colorless glass bottle, Type II Ph. Eur., sealed with an infusion stopper (bromobutyl rubber and an aluminium flip-off cap
- 50 ml solvent (water for injections) in a 50 ml colorless glass bottle, Type II Ph. Eur., sealed with an infusion stopper (halobutyl rubber) and an aluminium flip-off cap.
- 1 Octajet transfer device
- 1 particle filter

6.6 Special precautions for disposal and other handling

General Instructions

- The reconstituted solution should be almost colorless and slightly opalescent. Do not use solutions that are cloudy or have deposits.

Reconstitution

1. Warm both the powder (FIBRYGA) and the solvent (WFI) in unopened bottles up to room temperature. This temperature should be maintained during reconstitution. If a water bath is

used for warming, care must be taken to avoid water coming into contact with the rubber stoppers or the caps of the bottles. The temperature of the water bath should not exceed +37°C (98°F).

2. Remove the cap from the powder (FIBRYGA) bottle and the solvent to expose the central portion of the infusion stopper. Clean the rubber stoppers of both bottles with an alcohol swab and allow the rubber stopper of the bottles to dry.

3. Peel away the lid of the outer package of the Octajet transfer device. To maintain sterility, leave the Octajet device in the clear outer packaging.

4. Take the Octajet in its outer package and invert it over the powder (FIBRYGA) bottle. Place device while in the outer package onto the center of the powder bottle until the clips of the product spike (colorless) are locked. While holding onto the powder bottle, carefully remove the outer package from the Octajet, being careful to not touch the water spike (blue) and leave the Octajet attached firmly to the concentrate bottle. (Fig. 1)

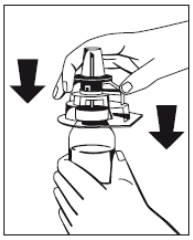

Fig. 1

5. With the powder (FIBRYGA) bottle held firmly on a level surface, invert the solvent bottle and place it at the center of the water spike. Push the blue plastic spike of the Octajet firmly through the rubber stopper of the solvent bottle. (Fig. 2)

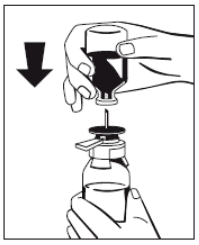

Fig. 2

6. Remove the distance ring (Fig. 3) and press the solvent bottle down (Fig. 4). Solvent will flow into the powder (FIBRYGA) bottle.

Fig. 3

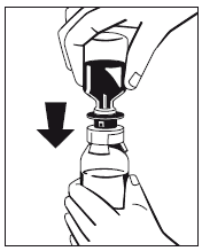

Fig. 4

7. When transfer of the solvent is complete, gently swirl the product bottle until the powder is fully dissolved. Do not shake the bottle to avoid foam formation. The powder should be dissolved completely within approximately 5 minutes. It should not take longer than 30 minutes to dissolve the powder. If the powder is not dissolved within 30 minutes the product should be discarded.

8. Turn the blue solvent bottle connector (both directions possible) to bring position markers together and remove solvent bottle together with the water spike. (Fig. 5)

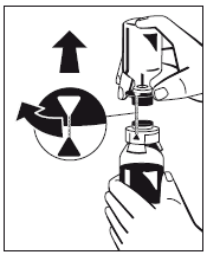

Fig. 5

9. Attach a syringe to the provided filter (Fig. 6) and connect the filter to the Octajet Luer Lock on the powder bottle (Fig. 7). Withdraw the solution through the filter into the syringe. (Fig. 8)

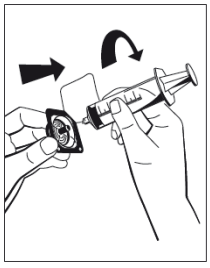

Fig. 6

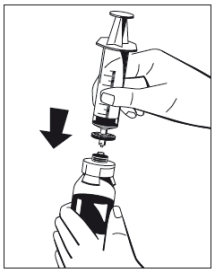

Fig. 7

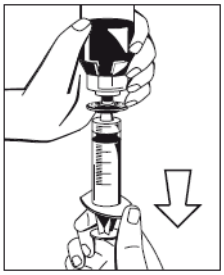

Fig. 8

10. Detach the filled syringe from the filter and discard the empty bottle.

A standard infusion set is recommended for intravenous application of the reconstituted solution at room temperature.

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

7. MARKETING AUTHORISATION HOLDER

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211, Henderson road;

#04-15 Henderson Building;

Singapore 159117

8. MANUFACTURER

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Octapharma AB, 112 75 Stockholm, Sweden

09. DATE OF REVISION OF THE TEXT

07/2020

10. LEGAL CATEGORY

For prescription only.