PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

FIBRYGA®

Fibrinogen Concentrate (Human)
Powder and Solvent for Solution for Injection / Infusion
1 g/vial reconstituted with 50 mL of diluent
ATC-Code: B02BB01

Manufactured by:
Octapharma Pharmazeutika Produktionsges. m.b.H.
Oberlaaer Strasse 235
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and
Octapharma AB
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Manufactured for:
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Submission Control No: 239501

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FIBRYGA®

Fibrinogen Concentrate (Human)

PART I: HEALTH PROFESSIONAL INFORMATION

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Intravenous use	Powder and Solvent for solution for injection / infusion 1 g/vial	Powder: Glycine, L-Arginine hydrochloride, Sodium chloride, Sodium citrate dihydrate Solvent: Water for Injection *For a complete listing see section* DOSAGE FORMS, COMPOSITION AND PACKAGING.

DESCRIPTION

FIBRYGA (Fibrinogen Concentrate (Human), 1 g/vial) is a sterile, freeze dried preparation of highly purified fibrinogen.

Solvent: 50 mL Water for Injection

After reconstitution with 50 mL Water for Injection, FIBRYGA contains approximately 20 mg/mL human fibrinogen.

FIBRYGA is prepared from large pools of human plasma employing precipitations, filtrations and chromatographic steps. Pathogen inactivation/removal is accomplished by a solvent detergent (S/D) method and nanofiltration (20 nm).

INDICATIONS AND CLINICAL USE

FIBRYGA is indicated for the treatment of acute bleeding episodes and perioperative prophylaxis in adult and pediatric patients with congenital afibrinogenemia and hypofibrinogenemia.

FIBRYGA may be used as a complementary therapy during the management of uncontrolled severe bleeding in patients with acquired fibrinogen deficiency in the course of surgical interventions (See Part II, CLINICAL TRIALS / Clinical Data in Acquired Fibrinogen Deficiency).

Geriatrics (>65 years of age):

Clinical studies of FIBRYGA included 184 subjects >65 years old. (See Part II, CLINICAL TRIALS)

Pediatrics (<18 years of age):

Clinical studies of FIBRYGA included 13 children (12–17 years). (See Part II, CLINICAL TRIALS)

No data are available in patients below 12 years of age.

CONTRAINDICATIONS

FIBRYGA is contraindicated in individuals who have manifested severe immediate hypersensitivity reactions, including anaphylaxis to FIBRYGA or its components.

WARNINGS AND PRECAUTIONS

General

Products made from human plasma may contain infectious agents, such as viruses and theoretically, the variant Creutzfeldt-Jakob disease (vCJD) agent that can cause disease. The risk that such products will transmit an infectious agent has been reduced by screening plasma donors for prior exposure to certain viruses, by testing for the presence of certain current virus infections, and by inactivating and/or removing certain viruses. Despite these measures, such products can still potentially transmit disease. There is also the possibility that unknown infectious agents may be present in such products. Individuals who receive infusions of blood or plasma products may develop signs and/or symptoms of some viral infections.

Allergic Reactions

Allergic reactions may occur. If symptoms of allergic or early signs of hypersensitivity reactions (including hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis) occur, immediately discontinue administration. The treatment required depends on the nature and severity of the reaction.

Thrombosis

There is a risk of thrombosis in patients with congenital or acquired fibrinogen deficiency receiving fibrinogen concentrates. Thrombotic events have been reported in patients receiving FIBRYGA. Weigh the benefits of FIBRYGA administration versus the risk of thrombosis. Patients receiving FIBRYGA should be monitored for signs and symptoms of thrombosis.

Special Populations

Pregnant Women: The safety of FIBRYGA for use in human pregnancy has not been established in controlled clinical trials. Animal studies have not been conducted to assess the safety with respect to reproduction, development of the embryo or fetus, the course of gestation and peri- and postnatal development. The benefits and risks of administrating FIBRYGA to pregnant women should be carefully weighed.

Nursing Women: The safety of FIBRYGA for use during lactation has not been established in controlled clinical trials and therefore should only be given with caution to breast-feeding mothers.

Monitoring and Laboratory Tests

Determination of the patient's fibrinogen level using an appropriate method, e.g., Clauss fibrinogen assay, is recommended before and during the treatment with FIBRYGA in order to avoid overdosing or underdosing.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

One serious adverse reaction has been reported in clinical studies with FIBRYGA so far: a case of thrombosis of moderate severity, described as ischemia due to digital microthrombi. Other serious adverse reactions that may potentially be observed for FIBRYGA are anaphylactic type reactions.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to the rate in the clinical trials of another drug and may not reflect the rates observed in practice.

The clinical safety of FIBRYGA was assessed in four studies in 394 patients with acquired fibrinogen deficiency (cardiac surgery or abdominal surgery), of whom one was aged 12 to <18 years, and 47 patients with congenital afibrinogenemia, of whom 12 were aged 12 to <18 years (see Part II, CLINICAL TRIALS). The adverse events (AEs) included sepsis, cerebrovascular accident, cardiac tamponade, hemorrhage, respiratory failure, acute kidney injury, renal failure, hallucinations, tachycardia, pleural effusion, nausea, vomiting, pyrexia, diarrhea, headache, nasopharyngitis and other respiratory tract infections and muscle pain.

Four mild AEs and one moderate AE were deemed possibly related to FIBRYGA. These AEs occurred in patients with congenital afibrinogenemia and included a case of mild pyrexia, two cases of mild skin reactions, a case of mild phlebitis and a case of moderate thrombosis (ischemia due to digital microthrombi), all of which resolved. A total of 247 serious adverse events were reported in 128 patients, of which one (the moderate case of thrombosis in congenital afibrinogenemia mentioned above) was considered related to the study drug.

Post-Market Adverse Drug Reactions

Three post-market adverse drug reactions have been reported for FIBRYGA: decreased systolic blood pressure, decreased blood pressure, and decreased oxygen saturation. In addition, the following adverse reactions have been identified during post-approval use of other fibrinogen concentrate products. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or to establish a causal relationship to fibrinogen products:

- Allergic/ anaphylactic reactions: anaphylaxis, dyspnea, rash, tachypnea, hypotension, shock and tachycardia
- Cardiovascular: thromboembolism, pulmonary embolism
- General: chills, fever, nausea, vomiting

DRUG INTERACTIONS

Overview

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

Drug-Drug Interactions

FIBRYGA should not be mixed with other medicinal products.

Drug-Food Interactions

Interactions with food have not been established.

Drug-Herb Interactions

Interactions with herbal products have not been established.

Drug-Lifestyle Interactions

Effects on ability to drive and use machines have not been established.

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment in Congenital Afibrinogenemia and Hypofibrinogenemia

FIBRYGA dosing, duration of dosing and frequency of administration should be individualized based on the extent of bleeding, laboratory values, and the clinical condition of the patient.

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.

In congenital afibrinogenemia and hypofibrinogenemia the recommended target fibrinogen plasma level is 100 mg/dL for minor bleeding or minor surgery and 150 mg/dL for major bleeding or major surgery.

FIBRYGA dose when baseline fibrinogen level is known

Dose should be individually calculated for each patient based on the target plasma fibrinogen level based on the type of bleeding, actual measured plasma fibrinogen level and body weight, using the following formula:

$$\text{Dose (mg/kg body weight)} = \frac{\text{[Target level (mg/dL) - measured level (mg/dL)]}}{\text{1.8 (mg/dL per mg/kg body weight)}}$$

FIBRYGA dose when baseline fibrinogen level is not known

If the patient's fibrinogen level is not known, the recommended dose is 60 mg per kg of body weight administered intravenously.

Monitoring of patient's fibrinogen level is recommended during treatment with FIBRYGA.

Recommended Dose and Dosage Adjustment in Acquired Fibrinogen Deficiency

The recommended initial dose for patients with uncontrolled severe bleeding in the course of surgical interventions is 4 g. Additional doses of 4 g are to be administered as needed to bleeding patients when fibrinogen plasma level is ≤200 mg/dL or 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.

Administration

For intravenous use only. Prior to use, allow FIBRYGA to reach ambient room temperature.

Do not use solutions that are cloudy or have deposits.

Reconstitution:

Vial Size	Volume of WFI to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
1 g	50 mL	50 mL	20 mg

1. Warm both the powder (FIBRYGA) and the solvent (Water for Injection, 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 stoppers 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 FIBRYGA bottle (Fig. 1).

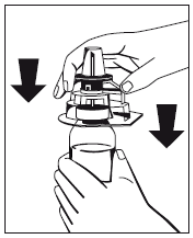

Fig. 1

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).

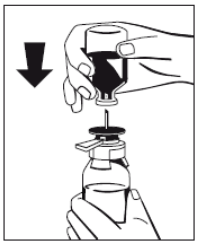

Fig. 2

6. While stabilizing the solvent bottle, remove the distance ring (Fig. 3). Press the solvent bottle down (Fig. 4). Solvent will flow into the powder (FIBRYGA) bottle.

Fig. 3

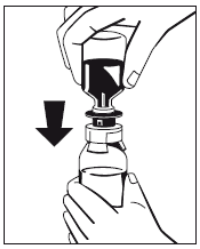

Fig. 4

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.

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).

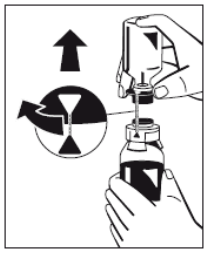

Fig. 5

9. While holding the provided filter in its outer package, attach a syringe to the filter (Fig. 6) and then 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).

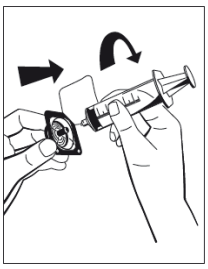

Fig. 6

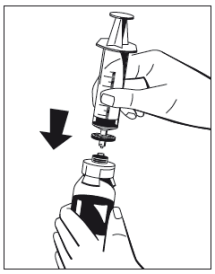

Fig. 7

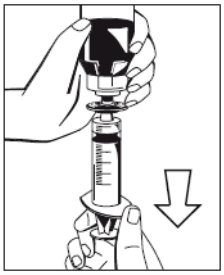

Fig. 8

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

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

FIBRYGA should be administered slowly intravenously at a recommended maximum rate of 5 mL per minute for patients with congenital afibrinogenemia and hypofibrinogenemia, and at a recommended maximum rate of 20 mL per minute during the management of uncontrolled severe bleeding in the course of surgical interventions for patients with acquired fibrinogen deficiency.

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

Precautions

FIBRYGA should not be mixed with other medicinal products. A separate intravenous line should be used for injection. Do not use the product after expiry date.

OVERDOSAGE

No cases of overdose have been reported.

For management of a suspected drug overdose, contact your regional Poison Control Center.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Fibrinogen (factor I) is a soluble plasma protein that, during the coagulation process, is converted to fibrin, one of the key components of the blood clot. Fibrinogen is a heterohexamer with a molecular weight of 340 kDa and composed of two sets of A*alpha*, B*beta*, and *gamma* polypeptide chains.

Following coagulation activation and thrombin generation, fibrinogen is cleaved by thrombin at specific sites on A*alpha* and B*beta* chains to remove fibrinopeptide A (FPA) and fibrinopeptide B (FPB). The removal of FPA and FPB exposes binding sites on fibrinogen and leads to the formation of fibrin monomers that subsequently undergo fibrin polymerization. The resulting fibrin is stabilized in the presence of calcium ions and by activated factor XIII. Factor XIIIa acts on fibrin to form cross links between fibrin polymers and renders the fibrin clot more resistant to fibrinolysis. The end product of the coagulation cascade is cross-linked fibrin which stabilizes the primary platelet plug and achieves secondary hemostasis.

Pharmacodynamics

Administration of FIBRYGA provides an increase in plasma fibrinogen level and can temporarily correct the coagulation defect of patients with congenital fibrinogen deficiency.

Pharmacokinetics

An open label, prospective, randomized, controlled, two-arm cross-over study was conducted in 22 patients with congenital fibrinogen deficiency (afibrinogenemia), ranging in age from 12 to 53 years (6 adolescents, 16 adults). In this cross-over study, these results were compared to the same parameters of another fibrinogen concentrate (RiaSTAP™) available in Canada in the same subjects. Each subject received a single intravenous 70 mg/kg dose of FIBRYGA and the comparator product. Blood samples were drawn from the patients to determine the fibrinogen activity at baseline and up to 14 days after the infusion. The pharmacokinetic parameters are summarized in Table 1. The mean values for the AUC_{norm} (primary endpoint) for fibrinogen activity following administration of FIBRYGA were significantly higher than after administration of RiaSTAP™.

No statistically relevant difference was observed between males and females for fibrinogen activity. In the per-protocol analysis, subjects less than 18 years of age (n=5) had small differences including a shorter half-life than in adults. The number of subjects less than 18 years of age in this study limits statistical interpretations.

The incremental in vivo recovery (IVR) was determined from plasma levels obtained up to 4 hours post-infusion. The mean incremental IVR for FIBRYGA was 1.8 mg/dL increase per mg/kg. The mean in vivo recovery indicates that a dose of 70 mg/kg will increase patients' fibrinogen plasma concentration by approximately 125 mg/dL.

Table 1: Pharmacokinetic Parameters (n=21) for Fibrinogen Activity				
Parameters	**FIBRYGA Activity Mean ± SD (range)**	**RiaSTAP™ Activity Mean ± SD (range)**	% Ratio of Geometric Means*	90% Confidence Interval Mean Ratio*†
Half-life [hr]	75.9± 23.8 (40.0–157.0)	69.4 ± 16.0 (48.6–101.9)	108.0	95.4, 122.4
C_{max} [mg/dL]	139.0 ± 36.9 (83.0–216.0)	126.5 ± 30.9 (85.0–199.0)	109.1	102.3, 116.2
AUC_{norm}	1.62 ± 0.45 (0.85–2.51)	1.38 ± 0.47 (0.76–2.46)	119.6	111.7, 128.1
Clearance [mL/hr/kg]	0.67 ± 0.20 (0.40–1.17)	0.80 ± 0.26 (0.41–1.31)	83.6	78.1, 89.5
Mean residence time [hr]	106.3 ± 30.9 (58.7–205.5)	99.0± 20.8 (72.4–141.2)	106.1	94.4, 119.2
Volume of distribution at steady state [mL/kg]	70.2 ± 29.9 (36.9–149.1)	76.6 ± 19.6 (47.9–113.7)	88.6	79.1, 99.4

* Geometric mean derived from the ANOVA model on log transformed values. †Not adjusted for multiplicity.
C_{max} = maximum plasma concentration; AUC_{norm} = area under the curve normalized to the dose administered;
SD = standard deviation

Absorption: Since FIBRYGA is administered intravenously, the product is available immediately. Bioavailability is proportional to the dose administered.

STORAGE AND STABILITY

FIBRYGA can be stored at +2°C to +25°C for up to 36 months from the date of manufacture. Do not use product after expiry date.

FIBRYGA contains no preservatives. Stability of the reconstituted solution has been demonstrated for up to 24 hours at +25°C. From a microbiologic point of view, unless the method of opening/reconstitution precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user. Discard partially used bottles.

Do not freeze. Protect from exposure to light. Keep in a safe place out of the reach and sight of children.

SPECIAL HANDLING INSTRUCTIONS

FIBRYGA should be inspected visually for particulate matter and discoloration prior to administration. Do not use non-homogenous solutions, or those that have a deposit. Any remaining fraction should be discarded. FIBRYGA should be warmed up to room or body temperature before use.

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

DOSAGE FORMS, COMPOSITION AND PACKAGING

To help ensure the traceability of biologic products, including biosimilars, health professionals should recognise the importance of recording both the brand name and the non-proprietary (active ingredient) name as well as other product-specific identifiers such as the Drug Identification Number (DIN) and the batch/lot number of the product supplied.

FIBRYGA is supplied in a single-use bottle containing the labeled amount of functionally active fibrinogen. The components used in the packaging for FIBRYGA are latex-free. FIBRYGA is a powder and solvent for solution for intravenous injection/ infusion.

The following dosage forms are available: 1 g

Nature and Contents of Container

Each vial of reconstituted FIBRYGA contains 1 g of the active ingredient human fibrinogen. Each package contains 1 glass bottle of human fibrinogen, 1 glass bottle of solvent (50 mL Water for Injection), a transfer device (Octajet), a particle filter and the package leaflet.

Composition:

Human Fibrinogen	1 g
Sodium chloride	300 mg
Sodium citrate dihydrate	75 mg
Glycine	500 mg
L-Arginine hydrochloride	500 mg

PART II: SCIENTIFIC INFORMATION

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: FIBRYGA®

Chemical name: Human Fibrinogen

Molecular formula and molecular mass: 340 kD

Structural formula: not applicable

Physicochemical properties: Fibrinogen is a soluble plasma glycoprotein of about 340 kD. The protein is a heterohexamer, composed of three pairs of polypeptides, namely two Aα–, two Bβ– and two γ–chains.

Product Characteristics

FIBRYGA (Fibrinogen [Human], 1 g/vial) is a sterile freeze dried preparation of highly purified fibrinogen derived from human plasma. It is prepared from large pools of human plasma employing precipitations, filtrations and chromatographic steps. Pathogen inactivation/removal is accomplished by a solvent detergent (S/D) method and a nanofiltration (20 nm).

Pathogen Safety

The pathogen safety of FIBRYGA is ensured through dedicated steps, in particular by the solvent/detergent treatment which inactivates enveloped viruses such as HIV, hepatitis B (HBV) and hepatitis C (HCV) virus and by nanofiltration (20 nm) for removal of both enveloped viruses and non-enveloped viruses such as hepatitis A virus (HAV) and parvovirus B19. Furthermore, the nanofiltration also removes potentially present infectious prion protein of an experimental agent of transmissible spongiform encephalopathy (TSE), considered a prudent model for Creutzfeldt-Jakob disease (CJD) and its variant form (vCJD).

CLINICAL TRIALS

Pharmacokinetic and functional activity study

An open label, prospective, randomized, controlled, two-arm cross-over study was conducted in 22 patients with congenital fibrinogen deficiency (afibrinogenemia), ranging in age from 12 to 53 years (6 adolescents, 16 adults). In this cross-over study, these results were compared to the same parameters of another Fibrinogen concentrate (RiaSTAP™) available in Canada in the same subjects. Each subject received a single intravenous 70 mg/kg dose of FIBRYGA and the

comparator product. Blood samples were drawn from the patients to determine the fibrinogen activity at baseline and up to 14 days after the infusion.

The pharmacokinetic study evaluated the single-dose PK (see Part I, ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics) and maximum clot firmness (MCF) in subjects with afibrinogenemia. MCF was determined by thromboelastometry (ROTEM®) testing and measured to demonstrate functional activity of replacement fibrinogen.

For each subject, the MCF was determined before (baseline) and one hour after the single dose administration of FIBRYGA or RiaSTAP™. The mean changes from pre-infusion to 1 hour post-infusion were 9.68 mm (95% CI: 8.37, 10.99) and 10.00 mm (95% CI: 8.07, 11.93), after administration of FIBRYGA or RiaSTAP™, respectively.

Safety and Efficacy Study in Congenital Afibrinogenemia and Hypofibrinogenemia

A prospective, open label, uncontrolled, multicenter phase 3 study was conducted in 25 patients with congenital fibrinogen deficiency (afibrinogenemia), ranging in age from 12 to 54 years (6 adolescents aged between 12 and 17 years, and 19 adults). Twenty-four patients were treated on-demand for 89 bleeding episodes and 9 patients underwent 12 surgical procedures. Of the 89 bleeding events (BEs), 67 (75.3%) were spontaneous and 22 (24.7%) were traumatic. There were 87 (97.8%) minor BEs and 2 (2.3%) major BEs.

For the treatment of the first bleeding episode, the patients received a median dose of FIBRYGA of 62.5 mg/kg (mean ± SD, 61.6 ± 16.93; range, 33.9–102.6 mg/kg) per infusion. The median number of infusions for BEs was 1 (range 1–7). A large majority of BEs (83/89, 93.3%) required only one infusion, with five BEs each being treated with two infusions. One BE, which was classed as major (occult gastrointestinal bleed), was treated with seven infusions. The median dose of FIBRYGA per infusion for treatment of all 89 BEs was 57.47 mg/kg (11.54–102.60).

Treatment was considered successful (rating of good or excellent efficacy) for 98.9% of BEs by an independent adjudication committee using an objective scoring system.

The efficacy of FIBRYGA for surgical prophylaxis was assessed in 12 surgical procedures in nine patients; 11 procedures were classified as minor and one was classified as major (eye enucleation with socket reconstruction). Median (range) loading FIBRYGA dose administered for all surgeries was 70 mg/kg (58.46–127.91). Five minor surgeries required between one and four additional intra- and/or postoperative infusions and the major surgery required seven additional post-operative infusions as per fibrinogen activity recommendations in the protocol. Median (range) FIBRYGA dose administered after the loading dose was 16.97 mg/kg (10.59–34.09). The overall success rate (rate of good or excellent efficacy) was 100% as assessed by the independent adjudication committee using an objective scoring system.

MCF was determined before (baseline) and one hour after the first FIBRYGA infusion for the first bleeding episode for each of the 24 patients. The observed mean change in MCF from baseline to 1 hour after the first infusion of FIBRYGA was 6.48 mm (SD=3.07).

One related serious adverse event was reported, a thrombosis of moderate severity, which was described as ischemia due to digital microthrombi. There were no reports of deaths or of severe allergic or hypersensitivity reactions. Three patients had positive anti fibrinogen antibody tests at baseline. In the other three patients, antibodies developed during the study. For one of these patients, these were still present at the end of the study. In the cases where the test indicated the presence of de novo antibodies, these did not appear to be neutralizing as there was no observable effect on fibrinogen levels or efficacy.

Clinical Data in Acquired Fibrinogen Deficiency

Data on FIBRYGA in acquired fibrinogen deficiency is available from a prospective, single-center, randomized, controlled, open-label phase 2 study assessing the hemostatic efficacy and safety of FIBRYGA compared with cryoprecipitate as sources of fibrinogen for patients with acquired fibrinogen deficiency undergoing major abdominal surgery, specifically cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for the peritoneal malignancy pseudomyxoma peritonei. Based on predicted average intraoperative blood loss $\geq$2 L, the first dose of FIBRYGA (4 g) or cryoprecipitate (two pools of five units each) was administered pre-emptively, while further doses of FIBRYGA or cryoprecipitate intraoperatively or during the first 24 hours postoperatively were administered as needed, based on bleeding and a FIBTEM A20 value of 12 mm or less.

A total of 45 patients were randomized and received treatment in the study: 22 patients who were randomized to receive FIBRYGA and 23 patients who were randomized to receive cryoprecipitate. Two patients (one in each treatment group) had a major protocol deviation related to dosing and were therefore excluded from analysis.

During the approximately 8 hours of surgery, a mean ± SD of 6.48 ± 2.96 g of FIBRYGA (representing 89.08 ± 38.884 mg/kg bw) or 4.09 ± 2.18 pools of five units of cryoprecipitate was administered per patient, respectively. For the FIBRYGA group, 21 patients received a total of 34 doses of 4 g each. For the Cryoprecipitate group, 22 patients received a total of 45 doses of 2 pools of 5 units / 400 mL each.

Hemostatic efficacy was based on a composite of the intraoperative hemostatic efficacy as assessed at the end of surgery and the postoperative hemostatic efficacy as assessed 24 hours after the end of surgery. In each case, a different objective 4-point hemostatic efficacy scale was used (excellent, good moderate, none) and was adjudicated by the Independent Data Monitoring & Endpoint Adjudication Committee (IDMEAC) based on a predefined algorithm. The algorithm classified overall treatment efficacy as “hemostatic success” or “hemostatic failure”. For all hemostatic efficacy adjudications, the IDMEAC was blinded to the treatment received by each patient.

Hemostatic therapy based on fibrinogen supplementation was rated as successful for 100% of the surgeries in both groups by the IDMEAC.

A median of 1 unit (range 0-4) and 0.5 units (range 0-5) RBC were administered intraoperatively to the patients treated with FIBRYGA and cryoprecipitate, respectively, with a median of 0 units (range 0-2) RBC during the first 24 hours postoperatively in both groups. No fresh frozen plasma or platelet concentrates were transfused during the study.

FIBRYGA was also investigated within a pragmatic, prospective, multicenter, randomized, controlled, single-blinded, phase 3 study conducted in adult cardiac surgical patients for whom fibrinogen supplementation was ordered in accordance with accepted clinical standards (significant hemorrhage and known or presumed hypofibrinogenemia). Hypofibrinogenemia was defined as fibrinogen plasma level <2.0 g/L by the Clauss method or FIBTEM-derived clot amplitude at 10-minutes (FIBTEM A10) <10 mm by thromboelastometry. Patients were randomly assigned to receive FIBRYGA, 4 g infused over approximately 10 minutes (infusion rate 20 mL per minute), or cryoprecipitate, 10 units infused according to local practice. The doses were to be repeated as needed.

A total of 827 patients were assessed for eligibility and were randomized to receive FIBRYGA (N=415) or cryoprecipitate (N=412). Of these, 32 patients in the FIBRYGA group and 29 patients in the cryoprecipitate group did not receive treatment due to cessation of bleeding and were excluded from analysis. In addition, 11 patients in the FIBRYGA group and 20 patients in the cryoprecipitate group were also excluded from analysis because consent could not be obtained. Overall, 735 patients, ranging in age from 17 to 88 years, were included in the analysis: 372 in the FIBRYGA group and 363 in the cryoprecipitate group. There was one patient <18 years of age, included in the FIBRYGA group. A total of 194 patients 18–65 years of age were included in the FIBRYGA group and 203 in the cryoprecipitate group, while 177 patients >65 years of age were included in the FIBRYGA group and 160 in the cryoprecipitate group. Concomitant administration of any therapies required as part of standard patient care was permitted including hemostatic drugs, Factor VIIa, Prothrombin Complex Concentrates, and tranexamic acid.

Patients received a median of 4 g (range 2.0–20.0) of fibrinogen concentrate and 10 units (range 10.0–120.0) of cryoprecipitate. The fibrinogen level increased from 1.722 ± 0.646 g/L to 2.454 ± 0.592 g/L in the FIBRYGA group and from 1.739 ± 0.583 g/L to 2.322 ± 0.578 g/L for the cryoprecipitate group, representing a mean increase of 0.850 ± 0.425 g/L in the FIBRYGA group and 0.692 ± 0.396 g/L in the cryoprecipitate group.

The mean ± standard deviation (SD) number of units of ABPs transfused in the FIBRYGA group during the first 24 hours after termination of cardio-pulmonary bypass was 16.3 ± 16.7 units (range 5.5–22.0 units). The mean ± SD number of units of ABPs transfused in the cryoprecipitate group was 17.0 ± 16.1 units (range 7.0–23.0 units).

TOXICOLOGY

Single Dose Toxicity

Two GLP-compliant single dose toxicity studies were performed with FIBRYGA in doses of up to 500 mg/ kg bw in rats and up to 1000 mg/ kg bw in mice. In both studies no mortality, no test item-related clinical signs and no macroscopic findings were observed.

Repeated Dose Toxicity

Repeated dose toxicity testing in animals with human protein preparations is impracticable due to the induction of, and the interference with antibodies. Therefore no studies were conducted with

FIBRYGA.

Reproductive Toxicity
No studies were conducted with FIBRYGA.

Local Tolerance
The local tolerance of FIBRYGA was tested in two studies after intravenous and intra-arterial and paravenous administration to rabbits. The animals were observed for 96 hours and then sacrificed for histological evaluation of the injection sites.

FIBRYGA was well tolerated, no general or relevant local changes, and no histological noticeable findings were observed.

Mutagenicity and Carcinogenicity
No studies were conducted with FIBRYGA.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PATIENT MEDICATION INFORMATION

FIBRYGA®
Fibrinogen Concentrate (Human)

Read this carefully before you start taking FIBRYGA and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about FIBRYGA.

What is FIBRYGA used for?

FIBRYGA is used for the treatment of acute bleeding episodes and perioperative prophylaxis in children and adults with congenital afibrinogenemia and hypofibrinogenemia. FIBRYGA may be used as a complementary therapy during the management of uncontrolled severe bleeding in patients with acquired fibrinogen deficiency in the course of surgical interventions.

How does FIBRYGA work?

FIBRYGA is a human fibrinogen presented as a powder for solution for intravenous administration (i.e. infusion into a vein). Fibrinogen is a normal constituent of the human blood and supports the blood coagulation of your body. Adequate doses of FIBRYGA may restore abnormally low fibrinogen levels to levels necessary for controlling bleeding.

What are the ingredients in FIBRYGA?

Powder:
Medicinal ingredients: Fibrinogen (Human)
Non-medicinal ingredients: Sodium chloride, Sodium citrate dihydrate, Glycine, L-Arginine hydrochloride

Solvent:
50 mL Water for Injection

FIBRYGA comes in the following dosage forms:

FIBRYGA is a powder and solvent for solution for intravenous injection and comes in the following dosage forms: 1 g

Do not use FIBRYGA if:

- you are allergic to human fibrinogen or any of the other ingredients contained in FIBRYGA.

- you have experienced allergic reactions to FIBRYGA in the past.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take FIBRYGA. Talk about any health conditions or problems you may have, including:

- Allergic reactions (e.g. reddening of the skin, skin rash, itching, fall in blood pressure, difficulty in breathing)
- General symptoms (e.g. chills, fever, nausea, vomiting)

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

The following may interact with FIBRYGA:

FIBRYGA should not be mixed with other products.

How to take FIBRYGA:

FIBRYGA is injected into a vein. The product should not be used if it looks cloudy or is leaking. It should be warmed up to room or body temperature before use. Discard any remaining contents after use. Do not use the product after its expiry date (printed on the bottle).

Reconstitution:

Vial Size	Volume of WFI to be Added to Vial	Approximate Available Volume	Nominal Concentration per mL
1 g	50 mL	50 mL	20 mg
1. Warm both the powder (FIBRYGA) and the solvent (Water for Injection, 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 stoppers 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 FIBRYGA bottle (Fig. 1).

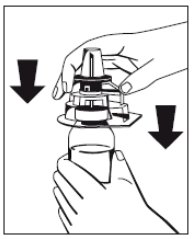

Fig. 1

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).

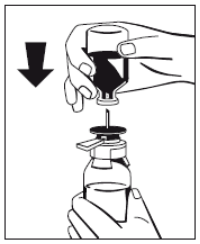

Fig. 2

6. While stabilizing the solvent bottle, remove the distance ring (Fig. 3). 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.

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).

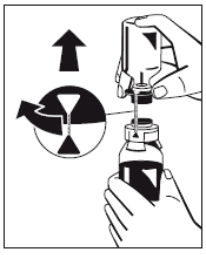

Fig. 5

9. While holding the provided filter in its outer package, attach a syringe to the filter (Fig. 6) and then 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).

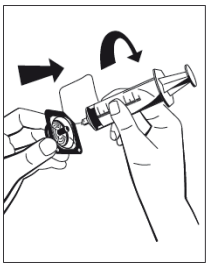

Fig. 6

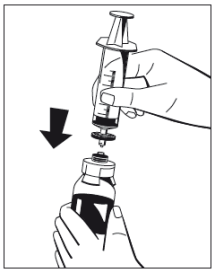

Fig. 7

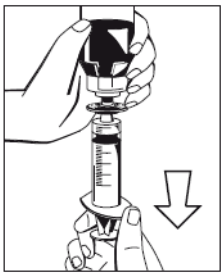

Fig. 8

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

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

FIBRYGA should be administered slowly intravenously at a recommended maximum rate of 5 mL per minute for patients with congenital afibrinogenemia and hypofibrinogenemia, and at a recommended maximum rate of 20 mL per minute for patients with acquired fibrinogen deficiency.

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

Usual dose:

Your doctor will determine the dose(s) of FIBRYGA. The dose and dosage regimen is dependent on the indication and may need to be individualized for each patient. Doses may be adjusted over time to achieve the desired clinical response and plasma fibrinogen levels.

Overdose:

No cases of overdose with human fibrinogen products have been reported.

If you think you have taken too much FIBRYGA, contact your healthcare professional, hospital emergency department or regional Poison Control Center immediately, even if there are no symptoms.

What are possible side effects from using FIBRYGA?

- The following side effects have been observed in studies with FIBRYGA: a case of mild pyrexia, two cases of mild skin reactions, a case of mild phlebitis and a case of moderate thrombosis.

The following side effects have been observed for other fibrinogen products and may potentially also occur after FIBRYGA administration:

- Allergic/ anaphylactic reactions: anaphylaxis, dyspnea, rash, tachypnea, hypotension, shock and tachycardia

- Cardiovascular: thromboembolism, pulmonary embolism
- General: chills, fever, nausea, vomiting

If any of the above listed symptoms occur, are severe or if they worry you, talk to your doctor or pharmacist. These are not all the possible side effects you may feel when taking FIBRYGA. For any unexpected effects while taking FIBRYGA, contact your doctor or pharmacist.
If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

Reporting Side Effects
You can help improve the safe use of health products for Canadians by reporting serious and unexpected side effects to Health Canada. Your report may help to identify new side effects and change the product safety information.
3 ways to report:
- Online at MedEffect;
- By calling 1-866-234-2345 (toll-free);
- By completing a Patient Side Effect Reporting Form and sending it by:
  - Fax to 1-866-678-6789 (toll-free), or
  - Mail to: Canada Vigilance Program
    Health Canada, Postal Locator 0701E
    Ottawa, ON
    K1A 0K9

  Postage paid labels and the Patient Side Effect Reporting Form are available at MedEffect.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:
Store at +2°C to +25°C for up to 36 months.
Do not freeze. Protect from light. Discard any remaining contents after use. Do not use after expiry date.

Keep out of reach and sight of children.

If you want more information about FIBRYGA:
- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website; the manufacturer's website http://www.octapharma.ca, or by calling 1-888-438-0488.

This leaflet was prepared by Octapharma Pharmazeutika Produktionsges.m.b.H

Last Revised: