Public Assessment Report

Riastap 1g

Human Fibrinogen

DE/H/1936/001/MR

MAH: CSL Behring GmbH

This module reflects the scientific discussion for the approval of Riastap 1g. The procedure has been finalised at 2010-07-27. For information on changes after this date please refer to the module 'Update'.

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1. INFORMATION OF THE INITIAL PROCEDURE

1. **Name of the product**
   Riastap

2. **Type of application**
   Full application according article 8.3 (i) Directive 2001/83/EC

3. **Active substance**
   Human Fibrinogen

4. **Form**
   Powder for solution for injection or infusion

5. **Strength**
   1 g (20mg/ml)

6. **Marketing Authorisation Holder**
   CSL Behring GmbH
   Emil-von-Behring-Str. 76
   35041 Marburg
   Germany

7. **Reference Member State**
   Paul-Ehrlich-Institut
   Germany

8. **Concerned Member States**
   BE, CY, DK, EL, ES, FI, FR, IE, IS, IT, LU, NO, PL, SE, SI, SK, UK

9. **Procedure-number**
   DE/H/1936/001/MR

10. **Timetable**

submission of application:	2010-04-14
start of procedure:	2010-04-28
termination of procedure:	2010-07-27

I.1 General comments on the submitted dossier

Riastap is a stand alone application according Art. 8(3) of Directive 2001/83 EC.

I.2 General comments on compliance with GMP, GLP, GCP and agreed ethical principles

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for the manufacture and assembly of Riastap.

II. RECOMMENDATION

Based on the review of data on quality, safety and efficacy, the RMS considers that the application for Riastap, in the indication"*Treatment of bleeding in patients with congenital hypo-, or afibrinogenaemia with bleeding tendency.*" can be approved. A national marketing authorisation was granted on 03 December 2009. The current approved trade name in Germany is Riastap 1g. The proposed name for the Mutual Recognition Procedure is Riastap.

III. SCIENTIFIC OVERVIEW

Quality

Riastap (Human Fibrinogen Concentrate, Pasteurized, HFCP), is a pasteurised human fibrinogen concentrate (powder for solution for injection or infusion) in a single one-gram dosage form and free from any preservatives. The HFCP container closure system consists of an infusion glass vial (Ph. Eur. quality) and a rubber stopper (Ph. Eur.) sealed with a combination crimp cap. It is stable for at least 60 months when stored at +2 to +25 °C. The product is manufactured by CSL Behring GmbH, Emil-von-Behring-Str. 76, 35041 Marburg Germany, and is the same medicinal product with an identical manufacturing process, identical qualitative and quantitative composition and identical pharmaceutical form as CSL Behring's Haemocomplettan P 1g.

HFCP contains albumin, L-arginine hydrochloride, sodium chloride and sodium citrate as excipients. HFCP is made from pooled human plasma that complies with the requirements of the Ph. Eur. monograph "Human Plasma for Fractionation" and with CSL Behring's Plasma Master File (PMF).

After reconstitution with 50 mL water for injection a colourless, clear to slightly opalescent solution is obtained, which contains 20 mg fibrinogen per mL. The reconstituted final product also has a relatively high concentration of the active component (18 - 26 mg of fibrinogen/mL) with a total protein content of 26 to 38 mg/mL. The concentrate is free from immunoglobulins and low in specific blood group isoagglutinins and can be used as a specific fibrinogen substitute in patients with congenital fibrinogen deficiency.

HFCP is manufactured in batches of 3,600 to 6,000 vials, corresponding to a final bulk volume of 180 to 300 kg. The fibrinogen is isolated and purified from human plasma (cryoprecipitate as starting material) in a continuous, well-controlled manufacturing process, eliminating efficiently protein and non-protein impurities. Critical process steps were identified in risk assessments and were qualified at full scale during process validation.

Process simulations with nutrient media demonstrated aseptic manufacturing conditions. To improve stability, the pure active ingredient is processed with minimal delay to the final bulk solution containing additional stabilizing excipients. A GMP compliant manufacturing environment is confirmed.

HFCP is a lyophilized concentrate. Development of the formulation was based on the inherently poor solubility of human fibrinogen derived from cryoprecipitation, purification and lyophilization. Significant improvements arose from the addition of L-arginine hydrochloride. Human serum albumin (Albumin 20 % or Alburex 25, both manufactured by CSL Behring) is added as stabilizer since it contributes significantly to the reconstitution characteristics and stability of freeze-dried proteins.
The data submitted demonstrate that the manufacturing process of Riastap fulfils the current state of the art criteria. All predefined acceptance criteria from different process validation studies were met and it is considered that the Riastap drug product manufacturing process has been successfully validated.

Adventitious Agents safety evaluation
The overall viral safety strategy includes selection of qualified donors and testing of plasma donations. Plasma is collected as specified in the current PMF. Single donations are screened by an adequate testing program for viral infections (Anti HIV, HBs-Ag and Anti-HCV). Further manufacturing pools are tested by NAT on HIV-RNA, HBV-DNA, HCV-RNA, HAV RNA and Parvovirus B19-DNA (limit: less than 10^4 IU B19-DNA per mL). Donors with an increased risk for sporadic or variant Creutzfelt-Jakob-Disease are excluded. The donor selection and plasma donation testing strategy for viral markers is considered adequate.
The drug substance is purified by several adsorption and precipitation steps which show a moderate capacity to reduce enveloped and non-enveloped viruses. Pasteurisation is performed at +60 °C for 20 h and effective inactivation of enveloped viruses as well as of non-enveloped viruses such as hepatitis A virus and Parvovirus B19 has been demonstrated.
In summary compliance with the requirements on virus safety as outlined in Guideline CPMP/BWP/269/95 has been demonstrated.

Non clinical
In view of the nature of product no conventional preclinical studies have been performed.
Non-clinical studies with HFCP include one pharmacodynamic and several toxicological studies.
The pharmacological in vivo profile of HFCP was shown in a hypofibrinogenemic rat model. In other studies (as referred to literature) efficiency of HFCP to overcome severe bleeding in a porcine dilutional and liver trauma model has been demonstrated.
A safety pharmacology study was done with HFCP intravenously administered in anesthetized dogs. In this study administration of HFCP was well tolerated in all animals, i.e. male as well as female animals. Minor changes in circulation and respiration were detected predominantly at the end of the observation period but were related to the narcosis procedure. Influences on hematological parameters (erythrocytes, white blood cells, platelets) were mild and transient, only.
Acute intravenous toxicity studies with single dose administration of HFCP were performed in mice and rats. The selected doses were 250, 500 and 1000 mg/kg b.w. (in mice) and 100, 200 and 300 mg/kg b.w. (in rats), respectively. In both studies administration of all dose levels were tolerated without any reported adverse reactions.
Local tolerance of HFCP was proven for intravenous (i.v.), intraarterial (i.a.) and paravenous (p.v.) administrations in a rabbit model.
Neoantigenicity studies after s.c. or i.v. administration of HFCP were performed in rabbits in order to determine if neoantigens might have been generated during the pasteurization process. But neoantigens could not be detected in the pasteurized HFCP product.

Thrombogenicity of HFCP was tested in a Wessler model in rabbits; HFCP did not demonstrate prothrombotic activity at doses up to 250 mg/kg.
In conclusion, given the type of product and the already long-lasting clinical experience, type and amount of preclinical studies are considered sufficient and further preclinical studies are not deemed necessary. The toxicological studies (including safety pharmacology) demonstrate that the dose intended for use in humans can be considered safe. The experience in humans since it was approved in 1986 also confirmed this conclusion.

Clinical
HFCP has been used in several countries to treat and prevent bleeding in patients with congenital fibrinogen deficiencies (afibrinogenemia, hypofibrinogenemia), and acquired hypofibrinogenemia.
Typically, 1 to 2 g fibrinogen is administered initially with subsequent infusions as required. In case of severe hemorrhage a dose of 4 - 8 g fibrinogen could be mandatory. This translates into doses calculated per kg body weight (based on a 70 kg patient) in a range of 15 - 30 mg/kg and maximal doses of 60 - 120 mg/kg.
Pharmacokinetic (PK) properties of HFCP were demonstrated in a pivotal Phase II study (BI3023_2001) investigating 15 patients with congenital afibrinogenemia (fibrinogen level of <20 mg/dL) and a supportive phase I study (BI3.023/7MN-101FM). PK findings were similar for fibrinogen activity and antigen. For the dose of 70 mg/kg b.w. the median half-life of fibrinogen activity was 77.1 h. Data of four children younger than 16 years displayed a shorter half-life and a faster clearance than adults.
The efficacy of HFCP to restore haemostasis in patients with congenital fibrinogen deficiency was documented in the GCP-conform pivotal trial (BI3023_2001) applying the surrogate endpoint maximum clot firmness (MCF), one clinical survey (CE1221_1) evaluating 100 subjects and one retrospective study of 12 patients (BI3.023/7MN-501FM). In this clinical program, HFCP showed the ability to correct for fibrinogen deficiency and restore the impaired clot firmness and clot formation based on the surrogate endpoint or on physician's judgment. In Study 2001, 1 hour after treatment with HFCP, median fibrinogen plasma activity and antigen levels were found to be 1.3 g/L. This is well within the recommended target of 1.0 to 1.5 g/L for patients with congenital fibrinogen deficiencies. This pivotal study also demonstrated that MCF 1 h after administration of HFCP was significantly higher compared to baseline. In addition, a post-marketing study is ongoing in order to confirm the efficacy of HFCP by showing an association between MCF increase and clinical efficacy based on the investigator's clinical assessment. Due to the rarity of disease and occurring bleeding situations this study is scheduled for 5 years. Furthermore, the clinical survey and the retrospective study (7MN-501FM) provided comparative data on the efficacy of human fibrinogen concentrate, cryoprecipitate and FFP in patients with congenital fibrinogen deficiency, in which cryoprecipitate and fibrinogen concentrate seem to be equally effective.
The safety profile of HFCP is considered satisfying. Generally, fibrinogen substitution is associated with an increased risk of thromboembolic events, allergic reactions and fever. In Study 2001, no clinical signs of thromboembolism or allergic reactions had been observed and none of the thrombogenicity marker levels were considered clinically significant by the investigator. Across four supportive studies only one thromboembolic event, one allergic event and two cases of fever have been reported. Thus, HFCP was well tolerated in the clinical program. Besides some related allergic-/anaphylactic cases and increases in body temperature, post-marketing experience (worldwide market between 1 January 1986 and 31 October 2008) displayed nine cases of thromboembolic events (8 possibly related, 1 insufficient data), which occurred mainly in patients with congenital fibrinogen deficiencies. There was no proven case of virus transmission and no reports of inhibitor development.
In conclusion, marketing authorisation was granted because of the long term clinical knowledge and of the overall clinical efficacy and the positive safety profile of HFCP.

IV. OVERALL CONCLUSION AND BENEFIT/RISK ASSESSMENT

The data on quality demonstrate that the manufacture of Riastap is considered to be state-of-the-art, including several process steps improving the virus safety of the product. Pasteurisation is performed at +60 °C for 20 h and effective inactivation of enveloped viruses as well as of non-enveloped viruses such as hepatitis A virus and Parvovirus B19 has been demonstrated.

The non-clinical studies (including safety pharmacology) demonstrated that the dose intended for use in humans can be considered safe.

The efficacy of HFCP to restore haemostasis in patients with congenital fibrinogen deficiency was documented in a GCP-conform pivotal trial applying maximum clot firmness (MCF) as surrogate efficacy endpoint, one clinical survey evaluating 100 subjects and a retrospective study on 12 patients. In this clinical program, HFCP showed the ability to correct for fibrinogen deficiency and restore the impaired clot firmness and clot formation based on the surrogate endpoint or on physician`s judgment. In Study 2001, 1 hour after treatment with HFCP, median fibrinogen plasma activity and antigen levels were found to be 1.3 g/L. This is well within the recommended target of 1.0 to 1.5 g/L for patients with congenital fibrinogen deficiencies. This pivotal study also demonstrated that MCF 1 h after administration of HFCP (70 mg/ kg b.w.) was significantly higher compared to baseline. In addition, a post-marketing study is ongoing to confirm the efficacy of HFCP by showing an association between the MCF increase and clinical response based on the investigator's clinical assessment.

Furthermore, the clinical survey and the retrospective study (7MN-501FM) provided comparative data on the efficacy of human fibrinogen concentrate, cryoprecipitate and FFP in patients with congenital fibrinogen deficiency, in which cryoprecipitate and fibrinogen concentrate seem to be equally effective. However, fibrinogen concentrates have the advantage of an efficient virus inactivation/elimination step and requiring reduced fluid infusion in comparison to cryoprecipitate or FFP.

The safety profile of HFCP is considered satisfying. Generally fibrinogen substitution is known to be associated with an increased risk of thromboembolic events, allergic reactions and fever. In Study 2001, no clinical signs of thromboembolism or allergic reactions had been observed and none of the thrombogenicity marker levels were considered clinically significant by the investigator. Across four supportive studies only one thromboembolic event, one allergic event and two cases of fever have been reported. Thus, HFCP was well tolerated in the clinical program. Besides some related allergic-/anaphylactic cases and increases in body temperature, post-marketing experience (worldwide market between 1 January 1986 and 31 October 2008) displayed nine cases of thromboembolic events (8 possibly related, 1 insufficient data), which occurred mainly in patients with congenital fibrinogen deficiencies. Apart from that, there was no proven case of virus transmission and no reports of inhibitor development.

Overall, the efficacy and safety of the product is considered to be adequately reflected within the clinical development program for Riastap.

After the evaluation of all the available quality, efficacy and safety data of Riastap a positive risk/benefit ratio can be concluded in the indication intended for clinical use.

V. PRODUCT INFORMATION

SUMMARY OF PRODUCT CHARACTERISTICS

NAME OF THE MEDICINAL PRODUCT

Riastap 1 g, powder for solution for injection / infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Riastap is presented as a powder for solution for injection or infusion containing 1 g human fibrinogen per vial.

The product reconstituted with 50 ml of water for injections contains approximately 20 mg/ml human fibrinogen.

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

Excipients recognised to have a known effect:
Sodium up to 164 mg (7.1 mmol) per vial.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection/infusion.
White powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of bleeding in patients with congenital hypo-, or afibrinogenaemia with bleeding tendency.

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.

Initial Dose
If the patient's fibrinogen level is not known, the recommended dose is 70 mg per kg of body weight (BW) administered intravenously.

Subsequent Dose
The target level (1 g/l) for minor events (e.g. epistaxis, intramuscular bleeding or menorrhagia) should be maintained for at least three days. The target level (1.5 g/l) for major events (e.g. head trauma or intracranial haemorrhage) should be maintained for seven days.

$$\text{Dose of fibrinogen (mg/kg body weight)} = \frac{\text{[Target level (g/l) - measured level (g/l)]}}{\text{0.017 (g/l per mg/kg body weight)}}$$

Dosage for neonates, infants and children
Limited data from clinical studies regarding the dosage of Riastap in children are available. Resulting from these studies, as well as from long lasting clinical experience with fibrinogen products, dosage recommendations in the treatment of children are the same as for adults.

Method of Administration
Intravenous infusion or injection.
Riastap should be reconstituted according to section 6.6. The reconstituted solution should be warmed to room or body temperature before administration, then injected or infused slowly at a rate which the patient finds comfortable. The injection or infusion rate should not exceed approx. 5 ml per minute.

4.3 Contraindications

Hypersensitivity to the active substances or to any of the excipients.

4.4 Special warnings and precautions for use

There is a risk of thrombosis when patients with congenital deficiency are treated with human fibrinogen concentrate, particularly with high dose or repeated dosing. Patients given human fibrinogen concentrate 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 concentrate should be weighed against the risk of thromboembolic complications. Caution and close monitoring should also be performed.

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.

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.

Riastap contains up to 164 mg (7.1 mmol) sodium per vial. This correlates with 11.5 mg (0.5 mmol) sodium per kg body weight of the patient if the recommended initial dose of 70 mg/kg body weight is applied. 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 and other pathogens.

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 (foetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g. haemolytic anaemia).

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

It is strongly recommended that every time that Riastap 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.

4.5 Interaction with other medicinal products and other forms of interaction

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

4.6 Pregnancy and lactation

Pregnancy:
Animal reproduction studies have not been conducted with Riastap (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 Riastap for use in human pregnancy has not been established in controlled clinical trials.

Clinical experience with fibrinogen concentrate 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 Riastap is excreted in human milk. The use of Riastap in lactating women has not been investigated in clinical trials.
A risk to the suckling child cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from Riastap therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility
There are no data on fertility available.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The following undesirable effects have been reported from post-marketing experience as well as scientific literature. The following standard categories of frequency are used:

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 (including reported single cases)

Organ class	Very common	Common	Uncommon	Rare	Very rare
Immune system disorders				allergic-anaphylactic reactions (such as generalised urticaria, rash, fall in blood pressure, dyspnoea)	
Vascular disorders					thromboembolic episodes including myocardial infarction and pulmonary

					embolism (see also section 4.4)
General disorders and administration site conditions				Increase in body temperature	

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

4.9 Overdose

In order to avoid overdosage, regular monitoring of the plasma level of fibrinogen during therapy is indicated (see 4.2).
In case of overdosage, 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 (F XIIIa) and calcium ions is converted into a stable and elastic three-dimensional fibrin haemostatic clot.

The administration of human fibrinogen concentrate provides an increase in plasma fibrinogen level and can temporarily correct the coagulation defect of patients with fibrinogen deficiency.

The pivotal Phase II study evaluated the single-dose PK (see 5.2 Pharmacokinetic properties) and also provided efficacy data using the surrogate endpoint maximum clot firmness (MCF) and safety data.
For each subject, the MCF was determined before (baseline) and one hour after a single dose administration of 70 mg/kg bw of Riastap. Riastap was found to be effective in increasing clot firmness in patients with congenital fibrinogen deficiency (afibrinogenaemia) as measured by thromboelastometry. Haemostatic efficacy in acute bleeding episodes, and its correlation with MCF, are being verified in a postmarketing study.

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 to 4 days. Regarding degradation, Riastap behaves like endogenous fibrinogen.

The product is administered intravenously and is immediately available in a plasma concentration corresponding to the dosage administered.

A pharmacokinetic study evaluated the single-dose pharmacokinetics before and after administration of human fibrinogen concentrate in subjects with afibrinogenaemia. This

prospective, open label, uncontrolled, multicenter study consisted of 5 females and 10 males, ranging in age from 8 to 61 years (2 children, 3 adolescents, 10 adults). The median dose was 77.0 mg/kg body weight (range 76.6 – 77.4 mg/kg).

Blood was sampled from 15 subjects (14 measurable) to determine the fibrinogen activity at baseline and up to 14 days after the infusion was complete. In addition, the incremental *in vivo* recovery (IVR), defined as the maximum increase in fibrinogen plasma levels per mg/kg body weight dosed, was determined from levels obtained up to 4 hours post-infusion. The median incremental IVR was 1.7 (range 1.30-2.73) mg/dl per mg/kg body weight. The following table provides the pharmacokinetic results.

Pharmacokinetic results for fibrinogen activity

Parameter (n=14)	**Mean ± SD**	**Median (range)**
$t_{1/2}$ [h]	78.7 ± 18.13	77.1 (55.73-117.26)
C_{max} [g/l]	1.4 ± 0.27	1.3 (1.00-2.10)
AUC for dose of 70 mg/kg [h•mg/ml]	124.3 ± 24.16	126.8 (81.73-156.40)
Extrapolated part of AUC [%]	8.4 ± 1.72	7.8 (6.13-12.14)
Cl [ml/h/kg]	0.59 ± 0.13	0.55 (0.45-0.86)
MRT [h]	92.8 ± 20.11	85.9 (66.14-126.44)
V_{ss} [ml/kg]	52.7 ± 7.48	52.7 (36.22-67.67)
IVR [mg/dl per mg/kg body weight]	1.8 ± 0.35	1.7 (1.30-2.73)

$t_{1/2}$ = terminal elimination half-life
h = hour
C_{max} = maximum concentration within 4 hours
AUC = area under the curve
Cl = clearance
MRT = mean residence time
V_{ss} = volume of distribution at steady state
SD = standard deviation
IVR = in vivo recovery

5.3 Preclinical safety data

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

Preclinical studies with repeated dose applications (chronic toxicity, cancerogenicity and mutagenicity) cannot be reasonably performed in conventional animal models due to the development of antibodies following the application of heterologous human proteins.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Human albumin,
L-arginine hydrochloride,
sodium hydroxide (for pH adjustment),

sodium chloride,
sodium citrate.

6.2 Incompatibilities

This product must not be mixed with other medicinal products, diluents or solvents except those mentioned in section 6.6. A standard infusion set is recommended for intravenous application of the reconstituted solution at room temperature.

6.3 Shelf life

5 years.

The physico-chemical stability for the reconstituted product has been demonstrated for 8 hours at room temperature (max. +25 °C). From a microbiological point of view the product should be used immediately following reconstitution. If the reconstituted product is not administered immediately, storage shall not exceed 8 hours at room temperature (max. +25 °C). The reconstituted product should not be stored in the refrigerator.

6.4 Special precautions for storage

Do not store above 25 °C. Do not freeze. Keep the vial in the outer carton, in order to protect from light.

6.5 Nature and contents of container

Vial of colourless glass, Type II Ph. Eur., sealed with a latex-free stopper (chlorobutyl rubber), aluminium cap and plastic disc.

Pack with 1 g
1 vial containing 1 g human fibrinogen

6.6 Special precautions for disposal and other handling

General instructions

- Reconstitution and withdrawal should be carried out under aseptic conditions.
- Reconstituted products should be inspected visually for particulate matter and discoloration prior to administration.
- The solution should be almost colourless to yellowish, clear to slightly opalescent and of neutral pH. Do not use solutions that are cloudy or have deposits.

Reconstitution

- Warm both the solvent and the powder in unopened vials to room or body temperature (not above 37 °C).
- Riastap should be reconstituted with water for injections (50 ml, not provided).
- Remove the cap from the Riastap vial to expose the central portions of the infusion stoppers.
- Treat the surface of the infusion stopper with antiseptic solution and allow it to dry.
- Transfer the solvent into the vial using an appropriate transfer device. Ensure complete wetting of the powder.

- Gently swirl the vial until the powder is reconstituted and the solution is ready for administration. Avoid strong shaking which causes formation of foam. The powder should be completely reconstituted within 15 minutes (generally 5 to 10 minutes).
- Reconstituted product should be administered immediately by a separate injection / infusion line.
- Take care that no blood enters syringes filled with product.

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

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

July 2010

Package leaflet: Information of the user

Riastap 1 g
Powder for solution for injection / infusion.
Human fibrinogen

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. WHAT RIASTAP IS AND WHAT IT IS USED FOR

What is Riastap?
Riastap contains human fibrinogen which is a protein important for blood clotting (coagulation). Lack of fibrinogen means that the blood does not clot as quickly as it should, which results in an increased tendency of bleeding. The replacement of human fibrinogen with Riastap will repair the coagulation mechanisms.

What is Riastap used for?
Riastap is used for treatment of bleeding in patients with a congenital lack of fibrinogen (hypo- or afibrinogenemia) with bleeding tendency.

2. BEFORE YOU USE RIASTAP

The following sections contain information that your doctor should consider before you are given Riastap.

Do NOT use Riastap:
- if you are hypersensitive (allergic) to human fibrinogen or any other ingredients of Riastap (see section *6. Further Information*).
  Please inform your doctor if you are allergic to any medicine or food.

Take special care with Riastap:
- if you have experienced allergic reactions to Riastap in the past. You should take antihistamines and corticosteroids prophylactically if advised by your doctor.

- when allergic or anaphylactic-type reactions occur (a serious allergic reaction that causes severe difficulty in breathing or dizziness). **The administration of Riastap should be stopped immediately (e.g. discontinue injection).**
- because of an increased risk of blood clots in a blood vessel (thrombosis), particularly:
  - in case of a high dose or repeated dosing
  - if you have had a heart attack (a history of coronary heart disease or myocardial infarction)
  - if you suffer from liver disease
  - if you have just had surgery (patients postoperatively)
  - if you will be having surgery soon (patients preoperatively)
  - in newborn infants (neonates)
  - if you are more likely to suffer from blood clots than normal (patients at risk of thromboembolic phenomena or disseminated intravascular coagulation)

Your doctor will consider carefully the benefit of treatment with Riastap compared with the risk of these complications.

Virus safety
When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include:
- careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded, and
- the testing of each donation and pools of plasma for signs of virus/infections.

Manufacturers of these products also include steps in the processing of the blood or plasma that can inactivate or remove viruses. Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV, the AIDS virus), hepatitis B virus and hepatitis C virus (inflammation of the liver), and for the non-enveloped hepatitis A virus (inflammation of the liver).

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 (infection of the unborn child) and
- for individuals whose immune system is depressed or who have some types of anaemia (e.g. sickle cell disease or haemolytic anaemia).

Your doctor may recommend that you consider vaccination against hepatitis A and B if you regularly/repeatedly receive human plasma-derived products.

It is strongly recommended that every time that Riastap is given, your doctor should record the date of administration, the batch number and the injected volume.

Taking other medicines
- Please tell your doctor or pharmacist if you are taking or have recently taken any medicines, including medicines obtained without a prescription.

- Riastap must not be mixed with other medicinal products except those mentioned in section "*The following information is intended for medical or healthcare professionals only / Reconstitution*".

Pregnancy and breast-feeding
- If you are pregnant or breast-feeding, please ask your doctor or pharmacist for advice before taking any medicine.
- During pregnancy and breast-feeding Riastap should be given only if it is clearly needed.

Driving and using machines
Riastap has no influence on the ability to drive and use machines.

Important information about some of the ingredients in Riastap
Riastap contains up to 164 mg (7.1 mmol) sodium per vial. This correlates with 11.5 mg (0.5 mmol) sodium per kg body weight of the patient if the recommended initial dose of 70 mg/kg body weight is applied. Please take this into account if you are on a controlled sodium diet.

3. HOW TO USE RIASTAP

Treatment should be initiated and supervised by a physician who is experienced in this type of disorder.

Dosage
The amount of human fibrinogen you need and the duration of treatment depend on:
- the severity of your disease
- the site and intensity of the bleeding
- the patient's clinical condition.

Overdose
Your doctor should regularly check your blood clot status during the treatment. In case of overdosage, the risk of development of thromboembolic complications is enhanced.

Method of administration
If you have any further questions on the use of this product, ask your doctor or pharmacist (see section *"The following information is intended for medical or healthcare professionals only"*).

4. POSSIBLE SIDE EFFECTS

Like all medicines, Riastap can cause side effects, although not everybody gets them.

Please contact your doctor immediately:
- **if any of the side effects occur**
- **if you notice any side effects not listed in this leaflet.**

The following side effects have been observed *rarely* (affects 1 to 10 users in 10,000):
- Increase in body temperature

- A sudden allergic reaction (such as reddening of the skin, skin rash over the whole body, fall in blood pressure, difficulty in breathing).

The following side effects have been observed *very rarely* (affects less than 1 user in 10,000):
- Risk of increased formation of blood clots (see section *2 "Take special care with Riastap"*).

5. HOW TO STORE RIASTAP

- **Keep out of the reach and sight of children.**
- Do not use Riastap after the expiry date, which is stated on the label and carton.
- Do not store above 25 °C.
- Do not freeze.
- Keep the vial in the outer carton, in order to protect from light.
- The reconstituted product should preferably be used immediately.
- If the reconstituted product is not administered immediately, storage shall not exceed 8 hours at room temperature (max. +25 °C).
- The reconstituted product should not be stored in the refrigerator.

6. FURTHER INFORMATION

What Riastap contains
The active substance is:
Human fibrinogen (1 g/vial; after reconstitution with 50 ml of water for injection approx. 20 mg/ml).
See section *"The following information is intended for medical or healthcare professionals only"* for further information.

The other ingredients are:
Human albumin, sodium chloride, L-arginine hydrochloride, sodium citrate, sodium hydroxide (for pH adjustment).
See last paragraph of section 2. "*Important information about some of the ingredients of Riastap*".

What Riastap looks like and contents of the pack
Riastap is presented as a white powder.
After reconstitution with water for injections the product should be clear or slightly opalescent, i.e. it might sparkle when held up to the light but must not contain any obvious particles.

Presentation
Pack with 1 g
1 vial containing 1 g human fibrinogen

Marketing Authorisation Holder and Manufacturer
CSL Behring GmbH
Emil-von-Behring-Strasse 76
35041 Marburg
Germany

This medicinal product is authorised in the Member States of the EEA under the following names:

Riastap 1 g powder for solution for injection/infusion	Slovenia
Riastap 1 g	Germany
Riastap	Cyprus, Denmark, Finland, France, Iceland, Ireland, Norway, Poland, Slovakia, Spain, Sweden, UK
T.b.d nationally	Belgium, Greece, Italy, Luxembourg

This leaflet was last approved in July 2010

The following information is intended for medical or healthcare professionals only

Posology

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.

Initial Dose
If the patient's fibrinogen level is not known, the recommended dose is 70 mg per kg body weight administered intravenously.

Subsequent Dose
The target level (1 g/l) for minor events (e.g. epistaxis, intramuscular bleeding, or menorrhagia) should be maintained for at least three days. The target level (1.5 g/l) for major events (e.g. head trauma, or intracranial haemorrhage) should be maintained for seven days.

$$\text{Dose of fibrinogen (mg/kg body weight)} = \frac{\text{[Target level (g/l) - measured level (g/l)]}}{\text{0.017 (g/l per mg/kg body weight)}}$$

Dosage for neonates, infants and children
Limited data from clinical studies regarding the dosage of Riastap in children are available. Resulting from these studies, as well as from long lasting clinical experience with fibrinogen products, dosage recommendations in the treatment of children are the same as for adults.

Method of Administration

General instructions
- Reconstitution and withdrawal should be carried out under aseptic conditions.
- Reconstituted products should be inspected visually for particulate matter and discoloration prior to administration.

- The solution should be almost colourless to yellowish, clear to slightly opalescent and of neutral pH. Do not use solutions that are cloudy or have deposits.

Reconstitution

- Warm both the solvent and the powder in unopened vials to room or body temperature (not above 37 °C).
- Riastap should be reconstituted with water for injections (50 ml, not provided).
- Remove the cap from the Riastap vial to expose the central portions of the infusion stoppers.
- Treat the surface of the infusion stopper with antiseptic solution and allow it to dry.
- Transfer the solvent into the vial using an appropriate transfer device. Ensure complete wetting of the powder.
- Gently swirl the vial until the powder is reconstituted and the solution is ready for administration. Avoid strong shaking which causes formation of foam. The powder should be completely reconstituted within 15 minutes (generally 5 to 10 minutes).
- Reconstituted product should be administered immediately by a separate injection/infusion line.
- Take care that no blood enters syringes filled with product.

Administration

A standard infusion set is recommended for intravenous application of the reconstituted solution at room temperature. The reconstituted solution should be injected or infused slowly at a rate which the patient finds comfortable. The injection or infusion rate should not exceed approx. 5 ml per minute.