Summary of Product Characteristics

1 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.

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

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 listed in section 6.1.

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 viruses HAV and parvovirus B19.

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 Fertility, 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 foetus.
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 foetus 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 or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Tabulated list of adverse drug reactions (ADRs)
The table combines the adverse reactions identified from clinical trials and post-marketing experience.
Frequencies presented in the table have been based on pooled analyses across two company sponsored, placebo-controlled clinical trials performed in aortic surgery with or without other surgical procedures [BI3023-2002 (N=61) and BI3023_3002 (N=152)] according to the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000).

For spontaneous post-marketing ADRs, the reporting frequency is categorised as 'Unknown'. In view of the fact that these trials were conducted in only the narrow population of aortic surgery, adverse drug reaction rates observed in these trials may not reflect the rates observed in clinical practice and are unknown for clinical settings outside the studied indication.

MedDRA SOC	**Undesirable effects**	**Frequency (In aortic surgery with or without other surgical procedures)**
General Disorders and Administration Site Condition	Pyrexia	Very common
Immune System Disorder	Anaphylactic reactions (including anaphylactic shock)	Uncommon
	Allergic reactions (including generalised urticaria, rash, dyspnoea, tachycardia, nausea, vomiting, chills, pyrexia, chest pain, cough, blood pressure decreased)	Unknown
Vascular Disorder	Thromboembolic events* (see section 4.4)	Common**

* Isolated cases have been fatal.
** Based on results of two clinical trials (aortic surgery with or without other surgical procedures), the pooled incidence rate of thromboembolic events was lower in fibrinogen treated subjects (N=8, 7.4%) compared with placebo (N=11, 10.4%).

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

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via:

UK: MHRA Yellow Card Scheme.
Website: www.mhra.gov.uk/yellowcard

IE: HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971;
Fax: +353 1 6762517. Website: www.hpra.ie; Email: medsafety@hpra.ie

Malta: ADR Reporting Website: www.medicinesauthority.gov.mt/adrportal

4.9 Overdose

In order to avoid over dosage, regular monitoring of the plasma level of fibrinogen during therapy is indicated (see 4.2).
In case of over dosage, 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, multicentre 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_{55} [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
C1 = clearance
MRT = mean residence time
V_{55} = 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

3 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 (bromobutyl rubber), aluminium cap and plastic disc.

Pack with 1 g *(Figure 1)*

1. One vial containing 1 g human fibrinogenF
2. Filter: Pall® Syringe Filter
3. Dispensing pin: Mini-Spike® Dispensing Pin

Figure 1

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).
- Wash hands or use gloves before reconstituting the product.
- 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. Generally, the powder dissolves within approximately 5 minutes. It should not take longer than 15 minutes to completely dissolve.
- Open the plastic blister containing the dispensing pin (Mini-Spike® Dispensing Pin) provided with Riastap (Figure 2).


Figure 2

- Take the provided dispensing pin and insert it into the stopper of the vial with the reconstituted product (Figure 3).


Figure 3

- After the dispensing pin is inserted, remove the cap. After the cap is removed, do not touch the exposed surface.
- Open the blister with the filter (Pall® Syringe Filter) provided with Riastap (Figure 4).

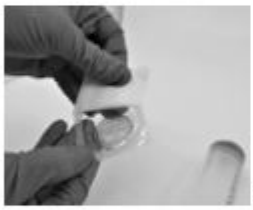
Figure 4

- Screw the syringe onto the filter (Figure 5).


Figure 5

- Screw the syringe with the mounted filter onto the dispensing pin (Figure

Figure 6

- Draw the reconstituted product into the syringe (Figure 7).


Figure 7

- When completed, **remove the filter, dispensing pin and empty vial from the syringe,** dispose of properly, and proceed with administration as usual.
- 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-Strasse 76
35041 Marburg
Germany

8 MARKETING AUTHORISATION NUMBER

PA0800/007/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 24th September 2010Date of last renewal: 3rd December 2014

10 DATE OF REVISION OF THE TEXT

September 2024