



**Australian Government**  

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**Department of Health and Ageing**  
**Therapeutic Goods Administration**

**Australian Public Assessment Report**  
**for**  
**Human Fibrinogen**

**Proprietary Product Name: RiaSTAP**  
**Submission No: PM-2009-01838-3-4**  
**Sponsor: CSL Limited**



**October 2010**

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## **I. Introduction to Product Submission**

### **Submission Details**

<i>Type of Submission</i>	New Chemical Entity
<i>Decision:</i>	Approved
<i>Date of Decision:</i>	2 August 2010
<i>Active ingredient(s):</i>	Human fibrinogen
<i>Product Name(s):</i>	RiaSTAP
<i>Sponsor's Name and Address:</i>	CSL Limited 189 – 209 Camp Road Broadmeadows Vic 3047
<i>Dose form(s):</i>	Powder for injection
<i>Strength(s):</i>	The labelled amount of RiaSTAP is 1 g of human fibrinogen. RiaSTAP reconstituted with 50 mL Water for Injections (20 mg/mL)
<i>Container(s):</i>	Type II clear glass vial
<i>Pack size(s):</i>	One vial per pack
<i>Approved Therapeutic use:</i>	Treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenaemia and hypofibrinogenaemia. There is limited experience with the use of the product for the treatment of congenital dysfibrinogenaemia (see Precautions).
<i>Route(s) of administration:</i>	Intravenous (IV) injection
<i>Dosage:</i>	Dosage and duration depend on the severity of the disorder. (If fibrinogen level is unknown the recommended dose is 70mg/kg body weight IV)
<i>ARTG Number (s)</i>	162828

### **Product Background**

Fibrinogen is a plasma coagulation factor crucial for blood clot formation. It exists as a dimer consisting of 3 pairs of polypeptide chains. In the circulation fibrinogen is a substrate for clot formation and stabilisation to fibrin through the action of thrombin and factor XIII. The control of clot size is through fibrin breakdown (fibrinolysis) by plasmin.

Congenital fibrinogen deficiency is a rare disorder characterised by bleeding episodes. Patients with the disorder can be classified as having afibrinogenaemia (complete absence), hypofibrinogenaemia (reduced levels) or dysfibrinogenaemia (abnormal fibrinogen molecule with reduced activity). The prevalence of the disorder is approximately 3 patients per million population, suggesting that there are probably less than 100 patients in Australia. Congenital afibrinogenaemia and hypofibrinogenaemia are very rare bleeding disorders caused by a deficiency or absence of fibrinogen presenting with non-surgical and postoperative excessive haemorrhage.

Dysfibrinogenaemia is caused by an abnormal fibrinogen molecule causing a functional defect that clinically either presents as a mild bleeding tendency or alternatively as an association with a

thrombotic event. Differentiation of the two extremes of the bleeding/thrombotic clinical presentation relies on the clinical and family history and molecular analysis of the gene defect.

Acquired deficiency of fibrinogen is much more common in clinical practice through either blood loss, excessive consumption through disseminated intravascular coagulation, infection, malignancy or ineffective production in end stage liver disease.

Therapy for fibrinogen deficiency includes cryoprecipitate, fresh frozen plasma and fibrinogen concentrates. However fresh frozen plasma and cryoprecipitate have safety and efficacy limitations because;

- potential for virus transmission on screened but not virally inactivated plasma
- volume overload for adequate fibrinogen replacement
- unnecessary protein infused (such as factor VIII/VWF in cryoprecipitate) that might contribute to thrombosis
- requirement for a blood bank and blood grouping of recipient
- potential allergic reactions and transfusion-related lung injury from plasma products.

Human Fibrinogen Concentrate Pasteurised (HFPCP) has been used since 1986 for fibrinogen replacement with documented safety and efficacy. This application formalises the registration of the product for use in Australia. As hereditary deficiency of fibrinogen is rare the number of patients for registration is limited.

RiaSTAP is a fibrinogen concentrate manufactured from human plasma. The plasma is sourced from donors in the US and Germany and the product is manufactured by CSL Behring in Germany. Manufacture of the product includes a heat treatment step for viral inactivation.

The product has been approved and supplied in various markets for many years under the tradename Haemocomplettan. An initial version of the product was marketed in the 1960's and the heat treatment step was introduced in 1985. The product has been supplied to a small number of patients in Australia under the Special Access Scheme.

There are no other fibrinogen concentrates registered in Australia. Alternative products used for the treatment of bleeding in patients with congenital fibrinogen deficiency are cryoprecipitate and fresh frozen plasma.

The proposed recommended initial dose is 70 mg/kg IV, with subsequent dosing determined according to the patient's measured fibrinogen level.

### **Regulatory Status**

The product has been designated as an Orphan Drug in Australia.

RiaSTAP (human fibrinogen) has been studied and registered under various trade names including Haemocomplettan P and RiaSTAP. The method of production is apparently unchanged during the product's development since the clinical studies since 1985. A similar application to the current Australian submission has been approved as Haemocomplettan P in Austria (June 1994), Bulgaria (January 2009), Czech Republic (March 1993), Germany (March 2005), Hungary (June 1998), Portugal (January 1978), Romania (July 1999), Switzerland (November 1992) and The Netherlands (March 1997) for the indication:

*Therapy and prophylaxis of haemorrhagic diatheses in:*

- *Congenital hypo-, dys- or afibrinogenaemia*
- *Acquired hypofibrinogenaemia resulting from*  
*- disorders of synthesis in cases of severe liver parenchyma damage*

- increased intravascular consumption e.g. as a result of disseminated intravascular coagulation, hyperfibrinolysis

- increased loss

*The most important clinical pictures associated with a defibrination syndrome are: Obstetrical complications, acute leukaemia especially promyelocytic leukaemia, liver cirrhosis, intoxications, extensive injuries, haemolysis after transfusion errors, operative interventions, infections, sepsis, all forms of shock as well as tumours especially in the lung, pancreas, uterus, and prostate.*

A similar application to the current Australian submission has been approved as RiaSTAP in Germany (December 2009) and RiaSTAP in the US (January 2008) for the respective indications:

*Treatment of acute bleeding in patients with congenital fibrinogen deficiency (Germany).*

*Treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenaemia and hypofibrinogenaemia. RiaSTAP is not indicated for dysfibrinogenaemia (US).*

An application was reviewed in the European Union (EU) under the Mutual Recognition Procedure (MRP) with Germany as the Reference Member State and 17 Concerned Member States. The MRP was positively closed on July 27, 2010. The indication agreed under the MRP is:

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

## **Product Information**

The approved product information (PI) current at the time this AusPAR can be found as Attachment 1.

## **II. Quality Findings**

### **Introduction**

Fibrinogen (blood coagulation factor I) is a soluble plasma glycoprotein dimer which consists of three pairs of polypeptide chains (A $\alpha$ , B $\beta$  and  $\gamma$ ). Fibrinogen is a physiological substrate of three enzymes: thrombin, factor XIII, and plasmin. During the coagulation process, the fibrinogen molecule forms fibrin which is cross-linked to provide tensile strength for the primary haemostatic platelet plug. In this document it is referred to as Human Fibrinogen Concentrate Pasteurized (HFCP).

HFCP is made from pooled human plasma that complies with the requirements of the European Pharmacopoeia monograph "Human Plasma for Fractionation" and with CSL Behring's Plasma Master File.

### **Plasma Master File**

The starting material for RiaSTAP is human plasma. The CSL Behring Plasma Master File supports the quality and suitability of the plasma used for the manufacture of RiaSTAP. The CSL Behring Plasma Master File 2009 Annual Update containing epidemiological data from 1 January-31 December 2008 was submitted and reviewed by the TGA and deemed acceptable on 12 February 2010.

### **Plasma Origin**

Only plasma sourced from the US and Germany is used in the manufacture of RiaSTAP. CSL no longer processes plasma from Austria. CSL commits to only using plasma that complies with variant Creutzfeldt-Jakob disease (CJD) donor deferral criterion given by the TGA, that is, donors who have lived in or visited the UK for a cumulative period of 6 months or more between 1 January

1980 and 31 December 1996 inclusive or who have received a transfusion of blood while in the UK from 1 January 1980 onwards are permanently deferred.

### **Drug Substance (active ingredient)**

The active ingredient present in HFCP is fibrinogen. The active ingredient is isolated and purified from human plasma for fractionation in a continuous manufacturing process. Due to limited stability, the pure active ingredient is directly processed to the final bulk solution, which contains additional stabilizing excipients. The final bulk may be stored for a period of 92 hours at +18 to +28°C.

The drug substance of HFCP is obtained after blending, final adjustment and sterilizing filtration of the bulk solution. No formal release specifications as such are established for the drug substance; however the in-process control requirements during manufacture of the bulk solution are equivalent to release specifications of the drug substance.

### **Drug Product**

#### **Presentation and formulation**

HFCP is a purified concentrate of fibrinogen. It is derived from human plasma and presented as a white powder for solution for injection. HFCP is a sterile, preservative free, lyophilized fibrinogen concentrate in a single-use 100 mL vial. The labelled amount of HFCP is 1 g of human fibrinogen. HFCP is reconstituted with 50 mL Water for Injections (20 mg/mL) and is administered intravenously. Each vial contains 900 to 1300 mg fibrinogen, 400 to 700 mg human albumin, 375 to 660 mg L-arginine hydrochloride, 200 to 350 mg sodium chloride and 50 to 100 mg sodium citrate. Sodium hydroxide and hydrochloride may be added to adjust the pH. It does not contain any preservatives. It is stable for at least 60 months when stored at +2 to +25 °C. After reconstitution with Water for Injections, the solution contains 20 mg fibrinogen per mL. Reconstituted HFCP is to be slowly infused via intravenous (IV) injection.

#### **Sterility safety**

There are no outstanding issues in regards to sterility aspects of the product.

#### **Container safety**

List of containers used for HFCP

<b>Presentation</b>	<b>Container</b>	<b>Stopper</b>	<b>Crimp Cap</b>
1 g	Infusion vial 100 mL, Type II glass	Chlorobutyl rubber 6322, gray	Combi cap, aluminum/polypropylene, red/light blue

There are no outstanding issues with regards to container safety.

#### **Endotoxin/pyrogen safety**

There are no outstanding issues.

#### **Viral/Prion safety**

The following three principal complementary approaches are used to prevent the potential viral/prion contamination of the final medicinal product:

- (i) selecting and testing the source material for the absence of detectable viruses
- (ii) testing the plasma pool for fractionation for the absence of viral contamination

(iii) virus inactivation and/or removal by the manufacturing process from which selected steps are tested in virus validation studies for their capacity to inactivate and/or remove viruses.

### **Non-viral adventitious agents**

The risk of transmitting prions, the causative agents of Creutzfeldt-Jakob disease (CJD) and related neurodegenerative disorders in animals and humans including variant CJD (vCJD), is negligible due to the fact that donors from UK or donors with a cumulative presence of more than 6 months in UK between 1980 and 1996 are excluded from donation.

The removal of prions (if present in the plasma pool) by two stages of the manufacturing process was shown in investigational studies.

### **Stability**

The stability study confirms a shelf-life of 60 months at a storage temperature of +2°C to +25 °C.

### **Quality Summary and Conclusions**

There were no objections to the registration of RiaSTAP on quality grounds.

## **III. Nonclinical Findings**

### **Introduction**

CSL Limited has applied to register a human fibrinogen (RiaSTAP) for the treatment of acute bleeding in patients with congenital fibrinogen deficiency. In support of the application, the sponsor submitted a primary pharmacology and a safety pharmacology study, single dose toxicity studies, local tolerance and antigenicity studies. All studies were conducted in the laboratories of CSL Behring's predecessor companies in Marburg, Germany over the period 1992-2004. As required, the safety pharmacology and toxicity studies were all Good Laboratory Practice (GLP)-compliant. The scope of studies is considered appropriate for this product. Due to the nature of the product (human origin), standard pharmacokinetic and toxicity studies with the proposed product in heterologous experimental species are not considered appropriate or necessary. Repeat-dose toxicity testing and embryofetal studies are impractical due to the induction of, and interferences by, antibodies.

### **Pharmacology**

#### **Primary pharmacology**

The *in vivo* pharmacological activity of HFCP was investigated in a rat disseminated intravascular coagulation (DIC) model. DIC was induced in rats by intravenous (IV) injection of the lipopolysaccharide (LPS) from *E. coli*. As a result of the consumption of coagulation factors, a decrease in the maximum amplitude (MA) and an increase in reaction time were seen in the thromboelastogram (TEG). As expected, increasing doses of HFCP led to increasing plasma levels of fibrinogen. A trend towards normalisation of TEG parameters was also seen at doses  $\geq 25$  mg/kg IV, suggesting a restoration of coagulation competency. HFCP has also been reported to improve coagulation parameters in a porcine model of dilutional coagulopathy<sup>1</sup>.

A DIC model, involving the consumption or loss of multiple coagulation factors, but still retaining the ability to synthesise more, is different to congenital fibrinogen deficiency. A congenital afibrinogenemic model, in which only fibrinogen is absent, would have been more appropriate. Such animal models are available<sup>2</sup>. Therefore, the submitted and published pharmacology studies

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<sup>1</sup> Fries, D., A. Krismer, A. Klingler, W. Streif, G. Klima, V. Wenzel, T. Haas and P. Innerhofer. Effect of fibrinogen on reversal of dilutional coagulopathy: a porcine model. *Br J Anaesth* 2005; 95: 172-177.

<sup>2</sup> Ploplis, V.A., J. Wilberding, L. McLennan, Z. Liang, I. Cornelissen, M.E. DeFord, E. D. Rosen and F.J. Castellino. (2000) A total fibrinogen deficiency is compatible with the development of pulmonary fibrosis in mice. *Am J Pathol* 2000; 157: 703-708.

do not directly support the proposed indication. However, some improvements in coagulation parameters were seen with RiaSTAP in the DIC model consistent with the expected pharmacology.

### **Safety pharmacology**

No adverse cardiovascular effects were observed in dogs at a cumulative dose of 320 mg/kg IV. The short period between doses (5 minutes) means the lower doses were not adequately tested. Minor effects on cardiovascular and respiratory parameters were seen predominantly at the end of the treatment period (30-60 minutes after the final treatment) and were suggested to be anaesthesia-related. Some changes in coagulation and fibrinolysis parameters were observed, consistent with the pharmacological activity and supraphysiological levels of fibrinogen, but there was no evidence of thromboembolic events.

### **Toxicology**

#### **General toxicity**

Two single dose toxicity studies were submitted. No test article-related mortalities, clinical signs or gross pathological findings were seen at the maximum tested doses; 1000 mg/kg IV in mice and 300 mg/kg IV in rats. These doses are far greater than those that would be expected clinically. There were no unanticipated toxicities.

#### **Local tolerance**

Local tolerance studies in rabbits indicated the clinical formulation was well tolerated after IV, intra-arterial (IA) and paravenous (PV) injection.

#### **Other Toxicity Studies**

No detectable neoepitopes were generated during the pasteurisation procedure. The death of one animal in the neoantigenicity studies was associated with anaphylactic shock, which is not unsurprising for a human protein provided to animals.

### **Nonclinical Summary and Conclusions**

A small, but adequate nonclinical dossier was submitted for this application.

In a rat disseminated intravascular coagulation model, RiaSTAP normalised fibrinogen levels and in the thromboelastogram assay, the maximum amplitude and reaction time. The response was dose-related and significant at doses  $\geq 25$  mg/kg IV.

No apparent treatment-related cardiovascular effects were observed in dogs at a cumulative dose of 320 mg/kg IV. Disturbances in coagulation parameters were attributed to pharmacological activity and supraphysiological fibrinogen levels.

Single dose toxicity studies were performed in rodents. There were no test article-related mortalities, clinical signs or gross pathological findings at doses up to 1000 mg/kg and 300 mg/kg IV in mice and rats, respectively.

RiaSTAP was shown to be well tolerated in rabbits after IV, IA and PV injection.

Neoantigenicity studies in rabbits (subcutaneous [SC] and IV administration) suggested no new epitopes were introduced in human fibrinogen during the pasteurisation process. The death of one animal in these studies was associated with anaphylactic shock.

While RiaSTAP has not been tested for efficacy in an appropriate nonclinical afibrinogenemic model, an improvement of coagulation parameters in a consumptive coagulopathy model lend support for the proposed indication.

Aside from thrombosis and anaphylaxis, which may be expected for this type of product, no additional safety concerns were identified in the submitted nonclinical studies.



There are no objections on nonclinical grounds to the registration of RiaSTAP for the proposed indication. However, due to the nature of the product (human origin), limited nonclinical data were submitted and safety and efficacy will need to be more comprehensively addressed by clinical data.

## **IV. Clinical Findings**

### **Introduction**

The studies used to support the application date from 1985 and are limited in providing reliable information on the safety and efficacy of RiaSTAP. The main reason for the lack of data is the rarity of the condition and the subjective dosing and reporting schedules used by the clinicians. Most studies were performed before Good Clinical Practice (GCP) and International Council on Harmonisation (ICH) guidelines were adopted.

Maximal clot firmness (MCF) with platelet inhibitors was used as a surrogate marker of efficacy and calculated by a central laboratory by thromboelastography (ROTEM). Although MCF is not as yet a prospectively clinically validated marker for outcome, it does provide an additional measure of performance of the HCFP to replicate normal fibrin formation. The clinical validation of MCF is proposed in the ongoing Study No. BI3023\_3001: A post marketing commitment study (prospective, open, historically controlled Phase IV study in 23 evaluable subjects) to validate an association between MCF and clinical efficacy of stopping acute bleeding. This study has an estimated duration of up to 60 months and is ongoing.

In seeking advice for registration in the EU, the sponsor indicated the following:

“In August 2007 CSL Behring requested scientific advice from the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) regarding the clinical development of HCFP for the treatment of acute bleeding in patients with congenital fibrinogen deficiency. A response to this request was provided in October 2007 and established the following:

Use of MCF seems to be an acceptable surrogate marker for haemostatic efficacy as proposed for the pivotal clinical study.

Given the extremely small population with congenital fibrinogen disorders with the limited possibility to perform adequate clinical studies, the fact that the pharmacological principle of fibrinogen supplementation is straight forward and the existence of retrospective safety and efficacy data, a commitment to conduct the proposed efficacy study post approval might be feasible.”

Accordingly, two new studies were initiated (one completed) and a clinician survey of current practice reported (CE 1221\_1). The new pharmacokinetic study BI3023\_2001 was performed in 2007-2008 and reported as the pivotal pharmacokinetic study utilising MCF and fibrinogen as surrogate endpoints.

A post marketing Study BI3023\_3001 is an ongoing prospective, open, historically controlled study in 23 evaluable subjects with afibrinogenaemia to validate an association between MCF and clinical efficacy of stopping acute bleeding. No updates of yearly reporting were included in the documentation and it would be appropriate to review the initial analysis if available.

The clinical efficacy endpoints of the definition of adequate fibrinogen rise rely mainly upon results derived from the clinical survey (CE1221\_1) and subjective clinician observations of efficacy in the other studies.

The Clauss method for fibrinogen estimation is the gold standard for pharmacokinetic studies and it is generally accepted levels greater than 1.0 to 1.5 g/L (100 to 150 mg/dL) are adequate for haemostasis. There are differences in unit measures of fibrinogen between the studies (mg/dL) and Australian practice (g/L). The formula for calculating the dose (mg per kg body weight) was

adapted to the Australian practice utilising the laboratory value of g/L in order to avoid any confusion in calculating the dose of RiaSTAP.

The safety data provides short rather than long term limited follow-up information in the target population of hereditary afibrinogenaemia. Formal viral safety data is very limited but the screening protocol for plasma used in RiaSTAP, the described purification and pasteurisation process and the significant log reduction of spiking experiments are the major known pathogens supports the product's viral safety. RiaSTAP long term post-marketing safety record since 1986 supports its safety from known viral infection.

The study (7D-501FM) with the largest number of patients (n=92) involves patients with acquired rather than hereditary disorders of fibrinogen. The data adds little to the indication for registration because the patients' conditions are heterogeneous, the dosing and reporting are not standardised and the fibrinogen consumption makes interpretation of fibrinogen increments difficult.

The main non-viral safety concern is the occurrence of thromboembolism after fibrinogen supplementation. Episodes of thrombosis have been reported and specifically patients at higher risk of venous or arterial disease are excluded from the studies. The cause of thrombosis could be as a result of the uncertainty of the appropriate dose of RiaSTAP and target fibrinogen level, the frequency of follow up dosing and the thrombotic phenotype of some forms of dysfibrinogenaemia. Expert opinion from the reported survey (CE 1221\_1) suggests the target peak of 1.5 g/L of fibrinogen is sufficient to treat major haemorrhage. The dosing recommendations of RiaSTAP will be confirmed in the post marketing study BI3023\_3001.

Dysfibrinogenaemia is not included in the indication for RiaSTAP approved in the EU and is actively excluded in the US registration since afibrinogenaemia, which is more regarded as a dysfunctional disease than a deficiency, is not supported by the clinical data. However, if the patient has a bleeding phenotype with dysfibrinogenaemia, then RiaSTAP is appropriate to consider, provided the dose is conservative and based on post-dose fibrinogen concentrations. In addition appropriate standard prophylaxis against venous thrombosis with major surgery should be strongly encouraged. This is also reflected in the wording of the approved therapeutic indication in Australia:

*Treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenaemia and hypofibrinogenaemia. There is limited experience with the use of the product for the treatment of congenital dysfibrinogenaemia (see Precautions).*

## **Pharmacodynamics**

It is assumed that RiaSTAP behaves like endogenous fibrinogen, the attributes of which have been described in the literature.

## **Pharmacokinetics**

Pharmacokinetic data were obtained from the pivotal study BI3.023\_2001 (n=15) and supported from study BI3.023/7MN-101(n=6). In BI3.023\_2001, 15 patients (14 evaluable) with afibrinogenaemia defined by a fibrinogen of less than 20 mg/dL were given a single 70 mg/kg dose of RiaSTAP and serial fibrinogen concentration (Clauss and antigenic method) and MCF were performed. In study BI3.023/7MN-101FM only 5/6 patients (one excluded because of high alanine transaminase [ALT] level) with afibrinogenaemia (defined by a fibrinogen of less than 80 mg/dL) were given a single dose of 60 mg/kg of RiaSTAP and serial fibrinogen concentrations (Clauss method) were performed.

Results are summarised in Table 1 and the course of fibrinogen increment shown in Figure 1.

Table 1: Pharmacokinetic Data for RiaSTAP

Variable	Median (range)	
	2001 <sup>a</sup>	7MN-101FM <sup>a</sup>
Terminal $t_{1/2}$ (h)	77.1 (55.73-117.26)	64.8 (60.0-88.8) <sup>b</sup>
$C_{max}$ (g/L)	1.3 (1.00-2.10)	not calculated
AUC <sup>c</sup> (days*kg) h*mg/mL	126.8 (81.73-156.40)	78.1 (51.24-79.30) <sup>b</sup>
Cl (mL/h/kg)	0.55 (0.45-0.86)	0.91 (0.84-1.22)
$V_{ss}$ (mL/kg)	52.7 (36.22-67.67)	89 (81-116)
MRT (h)	85.9 (66.14-126.44)	96.0 (79.2-100.8) <sup>b</sup>
Incremental IVR <sup>d</sup> ([mg/dL]/[mg/kg])	1.7 (1.30-2.73)	1.4 (1.13-1.49)
Classical IVR <sup>d</sup> (%)	61.8 (52.45-97.43)	54.1 (44.3-61.8)

<sup>a</sup> Data shown are from central laboratories in both studies. In Study 7MN-101FM the PK analysis population was used and in Study 2001 the PK PP population was used.

<sup>b</sup> In the original report for Study 7MN-101FM,  $t_{1/2}$  was 2.7 (2.5-3.7) days, MRT was 4.0 (3.3-4.2) days and AUC was 4.7 (3.05-4.72) days\*mg/dL standardized to the dose (mg) per kg b.w. For ease of comparison values given here were transformed from days into hours and from days\*mg/dL into h\*mg/mL, standardized to a dose of 70 mg/kg b.w.

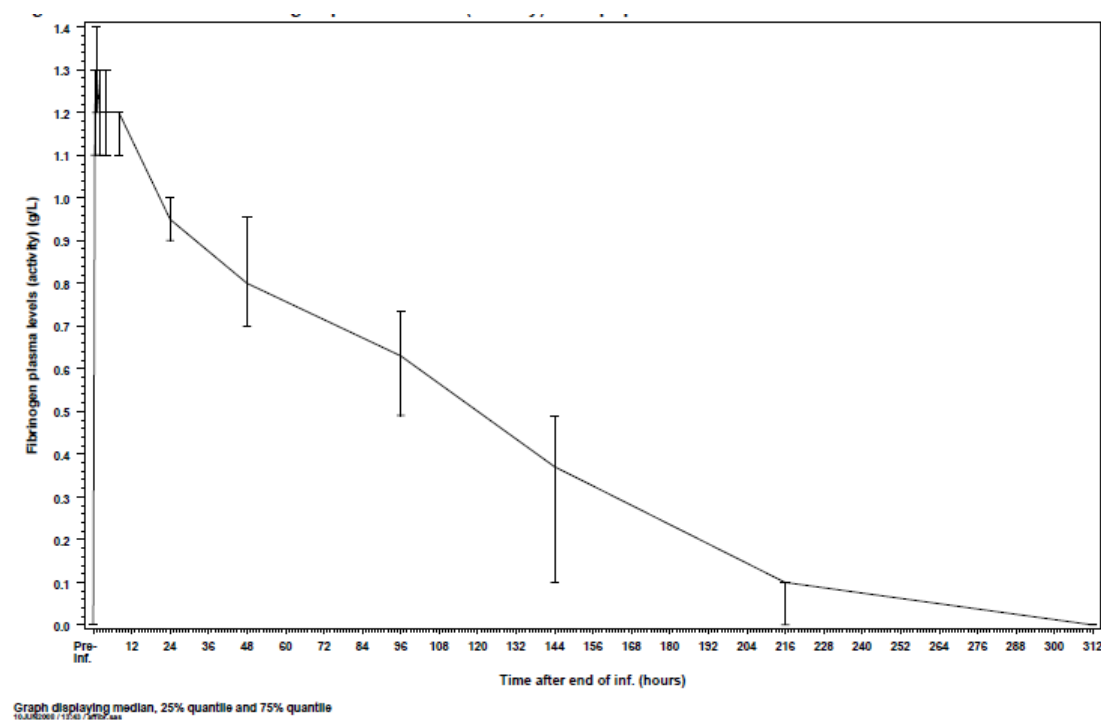
<sup>c</sup> Standardized to a dose of 70 mg/kg in Study 2001.

<sup>d</sup> Incremental IVR was referred to as response and classical IVR was referred to as recovery in Study 7MN-101FM.

AUC = area under the concentration-time curve; Cl = clearance;  $C_{max}$  = maximum concentration within 4 hours; h = hour(s); IVR = *in vivo* recovery; MRT = mean residence time; PK PP = pharmacokinetic analysis population;  $t_{1/2}$  = terminal elimination half-life;  $V_{ss}$  = volume of distribution at steady state.

Figure 1: Study 2001

Course of fibrinogen plasma activity - ITT population



The incremental *in vitro* recovery (IVR) of 1.7 mg/dL used for dosage calculations in the PI is based on the pivotal study B13.023\_2001. Four patients were under 16 years of age and had lower median terminal half-life ( $t_{1/2}$ ) (69.1 vs 82.4 hours), AUC (108.8 vs 149.1 h\*mg/mL) and MRT (74.7 vs 99.6 hours) but because of small sample size the clinical significance is uncertain.

Similar pharmacokinetic results were seen with either measures of fibrinogen antigen and activity in study B13.023\_2001.

Although not specifically designed for pharmacokinetic assessment, study B13.023/7MN-501FM also supported these finding with the median fibrinogen response (n=8) was 1.5 mg/dL per each substituted mg of fibrinogen/kg body weight (range 0.8 to 2.3 mg/dL). The median *in vivo* recovery (n=8) was estimated at 59.8 % (range 32.5 to 93.9 %).

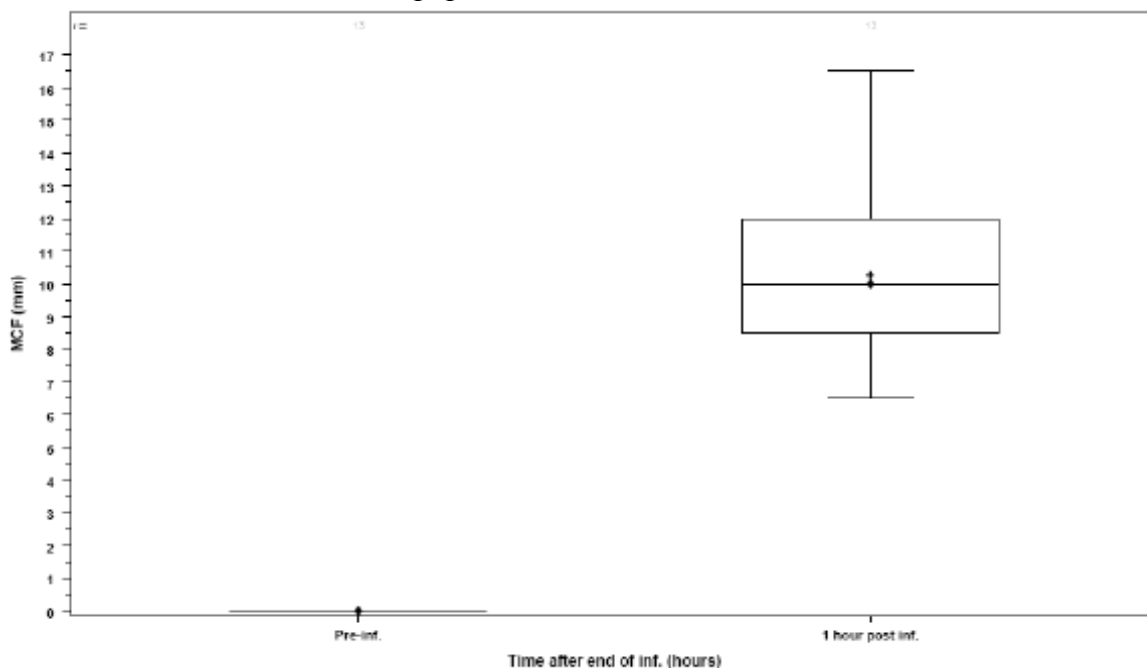
## Efficacy

A surrogate laboratory endpoint of MCF has been accepted by the EU as a marker of clinical efficacy but the correlation between MCF and clinical assessment for bleeding efficacy is lacking. This information is to be obtained in the yet to be published post-marketing Study BI3023\_3001.

Pivotal study B13.023\_2001 examined the change in MCF in 15 patients after 1 hour of infusion of 70 mg/kg of RiaSTAP. A convincing increment was found in MCF (from 0 mm to  $10.3 \pm 2.7$  mm (mean $\pm$ standard deviation [SD]) approaching the normal range for MCF found in the literature (median 14 mm; interquartile range 11-16 mm; range 4-22 mm).<sup>3</sup> Figure 2 shows the boxplot of the increment MCF in the ITT population.

Figure 2: Study 2001

Time course of MCF in the ITT population



Supportive data is found in the retrospective study B13.023/7MN-501FM where 12 patients were studied in 36 bleeding events including 11 during surgery (2 major). Subjective efficacy by the

<sup>3</sup> Rugeri L, Levrat A, David JS et al. Diagnosis of early coagulation abnormalities in trauma patients by rotation thromboelastography. J Thromb Haemost. 2007; 5: 289-95.

clinician following a dose of 62.8±33.9 mg/kg of HFCEP was good in all episodes with only one moderate grading in major surgery on the stomach. Prophylaxis was conducted in 89 episodes (in 86 subjects) with no breakthrough bleeding.

A clinical survey CE1221-1 was performed with 37 clinicians who treated 101 patients with hypo- and afibrinogenaemia. The information provides a snapshot of practice with most clinicians supporting a peak fibrinogen target of 100 mg/dL to 150 mg/dL for major haemorrhage or surgery. The range of treatment days of major haemorrhage/surgery was between 4-14 days and efficacy was similar between HFCEP and cryoprecipitate (greater than 90% good or excellent – Table 2).

Table 2: Study CE1221-1

Haemostatic efficacy by product and type of event

Product	Grade	Number of bleeds	%	Number of surgeries	%	Number of traumas	%
Fibrinogen	Excellent	56	39	32	70	24	40
	Good	76	53	13	28	34	57
	Poor	11	8	1	2	2	3
Cryo	Excellent	57	41	9	39	3	27
	Good	74	53	13	57	7	64
	Poor	8	6	1	4	1	9
Other	Excellent	4	31	2		1	
	Good	9	69	2		4	
	Poor	-	-			-	-

Study BI 3.023 / 7D-501FM was a clinical monitoring observational study in 92 patients with acquired hypofibrinogenaemia. The heterogeneity of the patients, the high mortality from the underlying illness, and the different mechanism of fibrinogen depletion/consumption make any interpretation of the data for this application for hereditary fibrinogen deficiency difficult. It does show that fibrinogen is increased after HFCEP from 75.9 mg/dL to 190 mg/dL and that haemorrhage was controlled in 49 patients (62%).

As HFCEP has been approved for use for many years before GCP and ICH guidelines were adopted, the study meeting these requirements for standard evaluation of efficacy has only just begun (BI3023\_3001). Its primary objective is to demonstrate the efficacy of Haemocompletan P administration by adequately controlling acute bleeding (spontaneous or after trauma) compared to the haemostatic efficacy data in the historical control on cryoprecipitate treatment from retrospective survey. Its secondary objective is to show an association of the clinical assessment of haemostatic efficacy and MCF. The dosing and target fibrinogen level is standardised and is the same as that for the proposed registration. The evaluator recommended that regular updates are reviewed by the TGA and undertakings are sought from the sponsor that the study will be completed post-registration. The evaluator also strongly recommended that a surgical study be undertaken to provide data on surgical efficacy of RiaSTAP in patients with fibrinogen deficiency.

## Safety

Safety data are very limited in the submission. The focus of the safety report is derived from the recent pharmacokinetic study B13.023\_2001 in 15 patients after a single standard dose. Other supporting studies are confounded by the retrospective design, non-standardised data collection, limited exposure to HFCEP and studies conducted before the introduction of GCP or ICH guidelines. Their usefulness for safety assessment is very limited. The study meeting these requirements for standard evaluation of safety has only just begun (BI3023\_3001) so it is an unusual process for

registration of a new product. However RiaSTAP has been used since 1985 in various countries and for individual patient approval so there is considerable experience worldwide with the product.

### Virus Safety

No convincing seroconversion has been demonstrated for 15 subjects in B13.023\_2001 or 6 patients in study 7D-402XX.RS. It supports the rigid donor selection, testing and inventory hold of sourced plasma and the virus inactivation steps which include pasteurisation. Theoretical experiments in virus validation studies also support that the manufacturing process which eliminates or inactivates relevant human pathogenic viruses as shown in Table 3.

Table 3: Virus Validation Studies

Virus Studied	Manufacturing stages studied / Scale reduction (% of manufacturing scale)				Mean Overall Virus Reduction
	Stage 1 0.03 to 0.3%	Stage 2 0.03 to 0.1%	Stage 3 reduction N/A	Stage 4 0.02%	
	Cryo- precipitation	Al(OH) <sub>3</sub> ads. / glycine ppt / Al(OH) <sub>3</sub> ads.	Pasteurization	1 <sup>st</sup> and 2 <sup>nd</sup> glycine ppt	
	log <sub>10</sub> ± SD (n) <sup>a</sup>	log <sub>10</sub> ± SD (n) <sup>a</sup>	log <sub>10</sub> ± SD (n) <sup>a</sup>	log <sub>10</sub> ± SD (n) <sup>a</sup>	log <sub>10</sub> ± SD <sub>cum</sub>
<b>Enveloped Viruses</b>					
HIV	n.d.	2.8 ± 0.0 (2)	≥ 5.7 (2)	3.9 ± 0.0 (2)	≥ 12.4
BVDV	n.d.	1.5 ± 0.3 (2)	≥ 9.1 (7)	2.1 ± 0.3 (3)	≥ 12.7
Herpesviruses <sup>b,c</sup>	1.6 ± 0.3 <sup>b</sup> (2)	[0.9] <sup>c</sup> (2)	≥ 8.1 <sup>c</sup> (5)	1.0 ± 0.3 <sup>c</sup> (2)	≥ 10.7
WNV <sup>d</sup>	n.d.	n.d.	≥ 8.3 (3)	n.d.	N/A
<b>Enveloped Viruses</b>					
HAV		2.4 ± 0.1 (2)	≥ 4.3 (2)	1.0 ± 0.3 (3)	≥ 7.7
CPV		2.8 ± 0.2 (2)	1.6 ± 0.0 (3)	1.6 ± 0.4 (2)	6.0 ± 0.3
B19V <sup>e</sup>	n.d.	n.d.	≥ 4.5 (3)	n.d.	N/A

## Other Safety Issues

Other adverse effects (AEs) in the studies were uncommon and summarised in Table 4.

Table 4: Adverse Effects in Study 2001, 7MN-101FM and 7D-501FM

<b>TEAEs by preferred term and system organ class (safety population Study 2001)</b>	
<b>System organ class</b>	<b>Number (%) of subjects</b>
<b>Preferred term (MedDRA)</b>	
<b>Number of subjects treated</b>	<b>15 (100)</b>
<b>Number of subjects with at least 1 TEAE</b>	<b>2 (13)</b>
Gastrointestinal disorders	1 (7)
Gastroesophageal reflux disease	1 (7)
General disorders and administration site conditions	1 (7)
Pain	1 (7)
Nervous system disorders	1 (7)
Headache	1 (7)
Respiratory, thoracic and mediastinal disorders	1 (7)
Epistaxis	1 (7)

MedDRA = medical dictionary for regulatory activities; TEAE = treatment-emergent adverse event.

### Adverse events in Study 7MN-101FM

<b>Subject number</b>	<b>Adverse event</b>	<b>Intensity</b>	<b>Causality</b>
101	Dyspnea	Mild	Possibly related
	Elevated temperature	Mild	Possibly related
301	Pain along the infused vein	Mild	Not related
	Headache	Mild	Not related
302	Pallor, nausea, shivering	Moderate	Not related
402	Dizziness, blood pressure 110/70 mmHg	Mild	Possibly related

### Adverse events in Study 7D-501FM

<b>Subject number</b>	<b>Adverse event</b>	<b>Intensity</b>	<b>Causality</b>
80	Fever	Moderate	Possibly related
81	Fever	Mild	Possibly related

A total of 20 subjects died during the course of Study 7D-501FM. None of these deaths, however, was considered related to HFCP substitution and reflected the serious nature of disorders of acquired fibrinogen depletion. One case of deep vein thrombosis occurred after high risk orthopaedic surgery in Study 7MN-501FM. No concerning changes in thrombogenicity markers were seen in Study 7MN-101FM as shown in Table 5.

Table 5: Changes in Thrombogenicity Markers in Study 7MN-101FM

Variable	Pre-infusion	Post-infusion			
		1 hour	4 hours	1 day	10 days
TT (sec)	120	20	20	24	56
PTT (sec)	200	42	41	47	74
Quick (%)	6	78	84	68	20
Fibrin monomer (nmol/L)	19	30	26	21	20
D-dimer (ng/mL)	5	40	63	53	20
F <sub>1+2</sub> (nmol/L)	1.1	1.1	2.3	1.4	1.2
TAT (µg/L)	3.5	5.0	5.1	2.6	2.6

F<sub>1+2</sub> = prothrombin fragment F<sub>1+2</sub>; PTT = partial thromboplastin time; TAT = thrombin-antithrombin III complex; TT = thrombin time.

No significant changes were noted in vital signs or haematological parameters. No inhibitors to fibrinogen were reported.

### Post-Marketing Data

Between January 1986 and October 2008, 1,034,389 g of HFCEP has been distributed and 49 spontaneous reports of adverse drug reaction have been received. Three deaths were reported, two were due to the underlying disease and one anaphylaxis unlikely related to HFCEP. The listings include expected AEs of allergic reactions and thromboembolic events and are detailed in Table 6.

Table 6: Adverse Effects Reported Post-Marketing

Adverse Drug Reaction	Number of Reported Cases	Number and Causality of Reported Cases
Allergic-allergoid/anaphylactic-anaphylactoid reaction (including generalized reactions such as chills, fever, nausea, vomiting)	20	16 possibly related, 3 insufficient data, 1 unrelated
Thromboembolic events	9	8 possibly related, 1 insufficient data
Suspected transmission of infectious disease	14	13 unrelated, 1 insufficient data
Lack of effect <sup>a</sup>	3	2 insufficient data, 1 unrelated

No proven virus transmission was identified.

### Clinical Summary and Conclusions

Hereditary fibrinogen deficiency is a very rare condition and it is appropriate that registration is considered for RiaSTAP. The clinical information is very limited for safety and efficacy and the ongoing and yet reported post marketing Study BI3023\_3001 will confirm the dosage recommendations in the PI. A surgical study "Safety and efficacy of prophylactic use of FCH in the peri-operative period in subjects with congenital fibrinogen deficiency." is planned and currently under review at the FDA. It is considered that these data are important for safe and effective use. It is strongly suggested a post registration surgical study following the PI dosing recommendations is initiated. The main safety concerns are allergy /anaphylaxis and thromboembolism. The risk of allergic reactions/anaphylaxis appears much less when compared to the alternate fresh blood products such as cryoprecipitate or fresh frozen plasma. It is interesting that dysfibrinogenaemia is excluded in the US registration of RiaSTAP and further clarification from the sponsor should be



sought for the reasons and regulatory discussions over the issue. If the patient has a bleeding phenotype with dysfibrinogenaemia, then RiaSTAP is appropriate to consider, provided the dose is conservative and based on post-dose fibrinogen concentration. In addition appropriate standard prophylaxis against venous thrombosis with major surgery should be strongly encouraged. It is estimated that the recruitment of patients for study BI 3023\_3001 will take approximately 60 months. The first study site was initiated in October 2009 but to date no subjects are enrolled in the study. Therefore no data on AEs are available at the present time. It is expected that recruitment of patients will be finalised in the second quarter of 2015. The final report will be available approximately 6 months later, that is, the fourth quarter of 2015

RiaSTAP also would theoretically appear to reduce the risk of viral infection when compared to cryoprecipitate because of the additional viral inactivation steps in the manufacturing process. As RiaSTAP has a long half-life; repeated dosing should be used cautiously as there is little safety and efficacy data particularly concerning the potential risk of thromboembolism with excessive accumulation of fibrinogen.

It was recommended that RiaSTAP be approved for registration whilst awaiting the results of the proposed studies.

## **V. Pharmacovigilance Findings**

### **Risk Management Plan**

The sponsor submitted a Risk Management Plan which was reviewed by the TGA's Office of Medicines Safety Monitoring (OMSM).

The sponsor identified following safety concerns:

#### Important identified risks:

- Allergic Reactions
- Transmissible Infectious Agents
- Thrombosis
- Undesirable Effects: Fever, Headache

#### Important potential risks and important missing information

- None identified

The OMSM reviewer noted that genotoxicity, carcinogenicity, reproductive, and developmental toxicity studies were not performed as human fibrinogen is a physiological constituent of the normal human plasma and adverse effects on reproductive functions or the foetus are not expected. It was stated that clinical experience with fibrinogen concentrate in treating obstetric complications suggests that no harmful effects on the course of the pregnancy or foetal or neonatal health are expected. There were no references to support this statement. It was considered that the sponsor should detail AEs in this patient population in the Periodic Safety Update Reports (PSURs).

Repeat-dose toxicology studies were not undertaken as human fibrinogen is a heterologous protein for experimental animals and unlikely to induce antibodies, and preclinical studies in humans are not feasible.

Paediatric use is anticipated. It was stated that clinical and post-marketing information suggests there are no differences in the safety and efficacy profiles as compared to adult subjects. Systematic investigation of efficacy and safety in the paediatric age group is not proposed. It was considered that the sponsor should detail AEs in this patient population in PSURs.

There have been few AE reports with HFPC. From January 1986 to August 2008, a total of 49 spontaneous AE reports had been received from the whole market. This included 20 with allergic

reactions and 9 with thromboembolic events. Of note, no cases of infection have been attributed to HFCP.

The OMSM noted that the sponsor considered that the safety of HFCP compares favourably with that of the alternate treatment options, fresh frozen plasma (FFP) and cryoprecipitate. It was noted that allergic reactions are less common with HFCP as the alternate therapies involve infusion of other proteins. Also, no virus inactivation /elimination occurs in the manufacture of most available FFP and cryoprecipitate. Hence, there is a theoretical higher potential risk of transmission. Treatment with HFCP has advantages as blood group matching is not required and the fibrinogen dose is inconsistent as its concentration in cryoprecipitate and FFP varies from donor to donor.

The OMSM noted that the sponsor stated that routine pharmacovigilance will be undertaken and this was accepted. The PSUR frequency was not stated. It was indicated that no post-approval studies are proposed in Australia but that a post-marketing study is currently recruiting patients in the US with its results to be available to CSL Limited and the TGA. This is a multinational, multicentre, prospective, open, historically controlled, Phase IIIb clinical trial to compare Haemocomplettan P efficacy to that of cryoprecipitate in subjects with afibrinogenaemia or severe hypofibrinogenaemia with acute minor or major bleeding requiring on demand treatment and to document its safety. No timeframe for the final report was provided and no interim report was planned. The safety variables being investigated include virus safety and AEs. Advice from the TGA's Office of Devices, Blood and Tissues indicates that the time frames for viral serology and PCR testing are appropriate. The protocol is comprehensive and includes the types and timeframes for patient examination, investigations and follow-up, data management and statistical analysis.

It was noted that the protocol specifies that Haemocomplettan P should not be refrigerated and should be administered immediately after reconstitution. This is different to the proposed RiaSTAP PI which states: "If it is not administered immediately, it must be stored below 25°C and used within 8 hours of reconstitution." This raises the question of whether the study will give information that is applicable to its use in the non-study setting and also whether use after 8 hours as per the PI is acceptable.

The Risk Minimisation Plan was accepted. The sponsor concluded that routine pharmacovigilance (including risk minimisation) activities are sufficient. It considered that medication errors are unlikely with HFCP use in Australia since 2006 and internationally since 1986 and physicians are familiar with its application and safety profile. Although the sponsor stated there was justification for routine risk minimisation activities, this was not presented.

The sponsor responded to the RMP evaluation and made the following point concerning PSUR frequency:

- The International Birth Date (IBD) of Haemocomplettan P is 1 February 1985. CSL Behring will issue a common PSUR for RiaSTAP and Haemocomplettan P according to the existing, harmonised 3-year PSUR cycle of Haemocomplettan P. The next 3-year PSUR will be available for submission in August 2010 and will report on the date period 1 July 2007 to 30 June 2010.

## **VI. Overall Conclusion and Risk/Benefit Assessment**

The submission was summarised in the following Delegate's overview and recommendations:

### **Quality**

There are no quality objections to registration. The application was considered by the Pharmaceutical Subcommittee (PSC) of the Advisory Committee on Prescription Medicines at its March 2010 meeting. No objections to registration were raised.

## Nonclinical

There were no nonclinical objections to registration. Only a limited preclinical data package was included in the submission. Single dose toxicity studies were conducted in mice and rats and no toxicities were observed.

## Clinical

### Clinical Evaluation

The clinical evaluator has recommended approval of the application. The sponsor has provided a response to the issues raised by the evaluator. In particular, the sponsor addressed two issues in the evaluator's conclusion:

CSL noted the TGA's comment regarding the absence of a proposed surgical study and agreed that data is important for the safe and effective use of RiaSTAP.

CSL advised the TGA that a study protocol is currently under review by the FDA (Protocol No.: BI3023\_4001, Title: "Safety and efficacy of prophylactic use of FCH in the peri-operative period in subjects with congenital fibrinogen deficiency.")

It is planned that patients undergoing minor surgery will be treated pre-operatively and peri-operatively to a target level of 100 mg/dL and patients undergoing major surgery will be treated to a target level of 150 mg/dL. The primary objective is assessment of excessive bleeding. Up to 15 subjects will be included in the study.

CSL also noted the TGA's comment regarding the exclusion of dysfibrinogenaemia in the US registration of RiaSTAP and provided the following clarification concerning the issue.

CSL Behring applied for the afibrinogenaemia, hypofibrinogenaemia and dysfibrinogenaemia indications for RiaSTAP in the USA; however, as noted by the TGA, the FDA has not accepted the proposed indication for dysfibrinogenaemia.

The exclusion of the dysfibrinogenaemia indication was not discussed in detail with the FDA. CSL Behring assumes that FDA's decision to exclude dysfibrinogenaemia from the registration was based on legal reasons, since the pivotal PK study (BI 3023\_2001) included only patients with afibrinogenaemia and therefore the FDA accepted the pivotal clinical study for the indications afibrinogenaemia and hypofibrinogenaemia but not for dysfibrinogenaemia.

However, CSL emphasised that RiaSTAP and Haemocomplettan are currently licensed in eight European countries and several non-European countries for all three indications: afibrinogenaemia, hypofibrinogenaemia and dysfibrinogenaemia.

The Delegate noted that the "pivotal" clinical study in the submission (**Study -2001**) was an open, single arm trial conducted in 15 patients with congenital afibrinogenaemia in 2007-08. Subjects were treated with a single dose (median = 77 mg/kg) IV. The study examined pharmacokinetics and a pharmacodynamic parameter (maximum clot firmness - MCF) as surrogate endpoints for clinical efficacy. The study has been published (*Journal of Thrombosis and Haemostasis* 2009).<sup>4</sup>

### Pharmacokinetics

In the pivotal study, administration of a single dose resulted in restoration of plasma fibrinogen levels to a concentration (1.3 g/L) just below the normal physiological range. Half-life was approximately 3.5 days and recovery was approximately 62%.

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<sup>4</sup> Manco-Johnson MJ, Dimichele D, Castaman G et al. Pharmacokinetics and safety of fibrinogen concentrate. *J Thrombosis Haemostasis* 2009; 7: 2064-2069.

Some additional PK data were available from a 1993 trial (**Study 7MN-101FM**) in which five subjects received a single dose of 60 mg/kg. Results were similar to those obtained in the pivotal study. Results for both studies are summarised in Table 1 of this AusPAR.

## Pharmacodynamics

The surrogate endpoint was MCF, as described in the study report for the pivotal study. MCF was measured at baseline and 1 hour after administration of RiaSTAP. MCF improved from 0 mm to  $10.3 \pm 2.7$  mm (mean  $\pm$  SD) as detailed in Table 7.

Table 7: MCF in the Pivotal Study

MCF [mm] (ITT population)						
Time point	N	Mean $\pm$ SD	Median (range)	Q <sub>25</sub>	Q <sub>75</sub>	P-value <sup>a</sup>
Pre-infusion	13	0 $\pm$ 0	0 (0-0)	0	0	--
1 hour post-infusion	13	10.3 $\pm$ 2.7	10.0 (6.5-16.5)	8.5	12.0	--
Mean change (primary analysis)	15 <sup>b</sup>	8.9 $\pm$ 4.4	9.5 (0-16.5)	7.0	12.0	<0.0001

ITT = intention-to-treat; MCF = Maximum clot firmness; Q<sub>25</sub> = 25% quantile; Q<sub>75</sub> = 75% quantile; SD = standard deviation.

<sup>a</sup> 2-sided p-value from one-sample t-test.

<sup>b</sup> The mean change was set to 0 for 2 subjects with missing MCF data.

According to the published version of the study, the normal range for this parameter is 14 – 30 mm.

## Efficacy

A study to assess the efficacy of the product using clinical efficacy endpoints is currently underway (**Study -3001**). The study will examine efficacy in patients with congenital afibrinogenemia or hypofibrinogenemia who present with an acute bleeding episode. Assessment of efficacy will include a comparison with historical data from patients treated with cryoprecipitate. The study will enrol 23 subjects and the sponsor anticipates that it will not be complete until 2015. The sponsor has indicated it will be preparing annual reports on the progress of the trial.

Other clinical efficacy data included in the submission were as follows:

Study **7MN-501FM** was a retrospective analysis of 12 patients treated with RiaSTAP between 1985 and 1992. These patients were treated for a total of 26 bleeding episodes and for 11 surgical procedures. There was no pre-specified dosage regimen. Median doses were 2.00 g per dose (range 0.2 – 8.0 g) and 4.00 g per total episode (range 0.2 – 16.0 g). Efficacy was rated by the treating physician as ‘very good’, ‘moderate’ or ‘poor’. Efficacy was rated as ‘very good’ in all 26 bleeding events and in 11 of 12 surgical procedures, with one procedure receiving a rating of ‘moderate’. This study has also been published (*Transfusion and Apheresis Science*, 2005).<sup>5</sup>

Study **CE1221-1** was a survey conducted between 2002 and 2003 of 37 clinicians in North America, Europe and Iran, who were involved in the treatment of 101 patients with congenital fibrinogen deficiency. Overall the respondents considered fibrinogen concentrates to be as effective as cryoprecipitate (Table 2).

## Safety

The primary evidence for safety comes from the post-marketing experience with the product. Between 1986 and 2008 only 49 spontaneous adverse event reports have been received by the sponsor. The main safety issues raised were thromboembolic events and allergic reactions.

<sup>5</sup> Kreuz W, Meili E, Peter-Salonen K et al. Efficacy and tolerability of a pasteurised human fibrinogen concentrate in patients with congenital fibrinogen deficiency. *Transfus Apher Sci* 2005; 32: 247-253.

In the pivotal study (n=15), two subjects reported four adverse events and in the retrospective study (n=12), four subjects reported 6 adverse events.

Viral and prion safety of the product has been found to be acceptable by the quality evaluator.

### **Risk Management Plan**

The proposed Risk Management Plan was evaluated by the TGA's Office of Medicines Safety Monitoring and was considered acceptable.

### **Risk-Benefit Analysis**

#### **Overall risk-benefit**

The data submitted to support registration were very limited. Assessment of efficacy essentially relies on pharmacokinetic data (restoration of fibrinogen activity in plasma) and pharmacodynamic data (effects on clot firmness). Viral safety has been satisfactorily established, but assessment of other safety issues essentially relies on post-marketing experience with the product. A clinical efficacy and safety study is in progress and the Delegate indicated that the advisory committee may wish to consider recommending rejecting the current application pending the outcome of this trial.

On the other hand, the condition being treated is very rare and therefore clinical trials are difficult to perform. The data from the ongoing study will not be available until 2015. As highlighted by the clinical evaluator, the alternative treatments available (cryoprecipitate, FFP) are associated with some significant safety issues when used for the treatment of bleeding in patients with congenital fibrinogen deficiency, including the risk of viral transmission.

On balance the Delegate believed it would be reasonable to approve the product based upon the limited submitted data, on the condition that annual reports of the ongoing study in patients with bleeding are provided, and the final report is submitted for evaluation when available.

#### **Use in congenital dysfibrinogenaemia**

The FDA has approved RiaSTAP but has excluded patients with congenital dysfibrinogenaemia from the approved indication. In its response to the clinical evaluation, the sponsor has stated that "*The exclusion of the dysfibrinogenaemia indication was not discussed in detail with the FDA*". The pivotal study in this application included only patients with afibrinogenaemia. The supportive retrospective study included only one patient with dysfibrinogenaemia. The ongoing clinical trial will only enrol patients with afibrinogenaemia or severe hypofibrinogenaemia.

Congenital dysfibrinogenaemia is a diagnosis that encompasses a diverse group of congenital abnormalities of the fibrinogen molecule. In some patients the particular mutation is associated with a tendency to thrombosis rather than bleeding. Given the lack of data in patients with dysfibrinogenaemia the Delegate considered that the restricted FDA indication is appropriate. If the advisory committee agrees that registration can be supported the Delegate proposed approval of the same indication wording as follows:

*Treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenaemia and hypofibrinogenaemia.*

*RiaSTAP is not indicated for dysfibrinogenaemia.*

In its response, the sponsor accepted the Delegate's position and agreed in part with the proposed indication. With regard to the statement "RiaSTAP is not indicated for dysfibrinogenaemia", the sponsor acknowledged that this was directly taken from the US product leaflet. However, the sponsor's preference was not to include this statement in the Australian Product Information. In the sponsor's opinion, the Indications section in the PI is intended to list all the approved indications for which the medicinal product is licensed. It is considered unusual to add statements for non-approved uses such as "RiaSTAP is not indicated for dysfibrinogenaemia" to this section.

Furthermore dysfibrinogenaemia is caused by a ‘dysfunction’ of the fibrinogen protein rather than a ‘deficiency’. Hence the requested indication for RiaSTAP is more accurately and adequately addressed by the following statement:

*Treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenaemia and hypofibrinogenaemia.*

### **Need for a surgical study**

The ongoing clinical study will examine the use of RiaSTAP in the treatment of acute bleeding episodes, either spontaneous or due to trauma. The study will not examine efficacy in patients undergoing surgery. The evaluator has recommended that a separate study be undertaken to examine efficacy in this setting. In its response to the clinical evaluation, the sponsor has indicated that such a study being planned.

The indication currently being sought by the sponsor is restricted to the treatment of bleeding episodes and therefore does not include use as prophylaxis in patients about to undergo surgical procedures. The draft product information (PI) also includes the following statement:

“In case of major surgical intervention, precise monitoring of replacement therapy by coagulation assays is essential”.

Given the limited indication currently being sought, and the advice from the sponsor that a surgical study is being planned, the Delegate did not consider that absence of such a study should be a barrier to registration. Text in the PI could be strengthened to emphasise the absence of data in the surgical setting.

The Delegate proposed to approve the application, with the restricted indication outlined above, and on the condition that annual reports of the ongoing clinical trial are provided, and that final reports of the ongoing study and the surgical study are submitted when available.

### **Advisory Committee Recommendation**

The Advisory Committee on Prescription Medicines (ACPM) (which has succeeded ADEC), having considered the evaluations and the Delegate’s overview, as well as the sponsor’s response to these documents, agreed with the sponsor’s proposal.

The ACPM recommended approval of the submission for the indication:

*Treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenaemia and hypofibrinogenaemia.*

The ACPM agreed that the registration should be conditional on the provision of annual reports on the ongoing clinical trials and that the additional ongoing and surgical studies are provided as soon as available.

Changes to the Product Information / Consumer Medicines Information which should be made prior to approval include:

Statements in the appropriate section/s about the very limited experience with use of the product for the treatment of congenital dysfibrinogenaemia, as some patients have an increased tendency to thrombosis, and that such use should only be undertaken by haematologists experienced in the treatment of coagulation disorders.

## **Outcome**

Based on a review of quality, safety and efficacy, TGA approved the registration of RiaSTAP powder for injection vial containing human fibrinogen 1g for the indication:

*Treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenaemia and hypofibrinogenaemia. There is limited experience with the use of the product for the treatment of congenital dysfibrinogenaemia (see Precautions).*

The following three conditions of registration were included:

1. The implementation of the Risk Management Plan as agreed to with the Office of Product Review (which has replaced the Office of Medicines Safety Monitoring).
2. Annual updates for the Plasma Master File are provided as per the format outlined in the guideline EMEA/CPMP/BWP/3794/03 “Note for Guidance on the Scientific Data Requirements for a Plasma Master File (PMF)”
3. The first five batches of RiaSTAP (AUST R 162828) imported into Australia are not released for sale until: (1) samples of each batch have been tested and approved by OLSS, and (2) the manufacturer’s release data have been evaluated and approved by OLSS. These batch release conditions will be reviewed and may be modified on the basis of actual batch quality and consistency. The sponsor may also be required to provide evidence of satisfactory shipping conditions to Australia for every batch imported. These conditions remain in place until the sponsor is notified officially in writing of any change.

Three vials of the last five batches should be provided for testing by OLSS together with any necessary standards, impurities and active pharmaceutical ingredients (together with their Certificates of Analysis) for method development and validation.

## **Attachment 1. Product Information**

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at [www.tga.gov.au](http://www.tga.gov.au).

## RiaSTAP<sup>®</sup>

### Australia

#### NAME OF THE MEDICINE

Human Fibrinogen, powder for injection.

#### DESCRIPTION

RiaSTAP<sup>®</sup> is a freeze-dried fibrinogen (coagulation factor I) concentrate derived from human plasma. It contains 1 g of human fibrinogen per vial. It is produced as a sterile white powder for intravenous injection after reconstitution with Water for Injections.

Pasteurisation (at +60°C for 20 hours) and multiple precipitation and absorption steps in the RiaSTAP<sup>®</sup> manufacturing process reduce the potential for pathogen transmission.

Each vial of RiaSTAP<sup>®</sup> contains the ingredients listed in **Table 1**.

**Table 1: Ingredients**

Fibrinogen	900 to 1300 mg
Albumin	400 to 700 mg
Arginine hydrochloride	375 to 660 mg
Sodium chloride	200 to 350 mg
Sodium citrate	50 to 100 mg

#### PHARMACOLOGY

Human fibrinogen in the presence of thrombin, activated coagulation factor XIII (FXIIIa) and calcium ions is converted into a stable and elastic three-dimensional fibrin haemostatic clot.

The administration of human fibrinogen concentrate provides an increase in plasma fibrinogen level and can temporarily correct the coagulation defect of patients with fibrinogen deficiency. The product is administered intravenously and is immediately available in a plasma concentration corresponding to the dosage administered.

#### Pharmacokinetics

A pharmacokinetic study evaluated the single-dose pharmacokinetics before and after administration of human fibrinogen 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 evaluable) 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 17 (range 13.0 - 27.3) mg/L per mg/kg body weight. **Table 2** provides the pharmacokinetic results.



**Table 2: Pharmacokinetic results for fibrinogen activity**

Parameter (n=14)	Mean ± SD	Median (range)
t <sub>1/2</sub> [h]	78.7 ± 18.13	77.1 (55.73-117.26)
C <sub>max</sub> [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 <sub>ss</sub> [mL/kg]	52.7 ± 7.48	52.7 (36.22-67.67)
IVR [mg/L per mg/kg body weight]	18 ± 3.5	17 (13.0 – 27.3)

t<sub>1/2</sub> = terminal elimination half-life  
h = hour  
C<sub>max</sub> = maximum concentration within 4 hours  
AUC = area under the curve  
Cl = clearance

MRT = mean residence time  
V<sub>ss</sub> = volume of distribution at steady state  
SD = standard deviation  
IVR = *in vivo* recovery

## CLINICAL TRIALS

### Efficacy and Safety

The pharmacokinetic study evaluated the single-dose pharmacokinetics and maximum clot firmness (MCF) in subjects with afibrinogenaemia. MCF was determined by thromboelastometry (ROTEM) testing. MCF was measured to demonstrate functional activity of replacement fibrinogen when a fixed dose of RiaSTAP<sup>®</sup> was administered. Clot firmness is a functional parameter that depends on: activation of coagulation, fibrinogen content of the sample and polymerisation/crosslinking of the fibrin network. Thromboelastometry has been shown to be a functional marker for the assessment of fibrinogen content and for the effects of fibrinogen supplementation on clinical efficacy.

For each subject, the MCF was determined before (baseline) and one hour after the single dose administration of RiaSTAP<sup>®</sup>. RiaSTAP<sup>®</sup> was found to be effective in increasing clot firmness in patients with congenital fibrinogen deficiency (afibrinogenaemia) as measured by thromboelastometry. The study results demonstrated that the MCF values were significantly higher after administration of RiaSTAP<sup>®</sup> than at baseline (see **Table 3**). The mean change from pre-infusion to 1 hour post-infusion was 8.9 mm in the primary analysis (9.9 mm for subjects < 16 years old and 8.5 mm for subjects ≥ 16 to < 65 years old). The mean change in MCF values closely approximated the levels expected from adding known amounts of fibrinogen to plasma *in vitro*.

**Table 3: Maximum Clot Firmness [mm] (Intention To Treat population)**

Time point	n	Mean ± SD	Median (range)
Pre-infusion	13	0 ± 0	0 (0-0)
1 hour post-infusion	13	10.3 ± 2.7	10.0 (6.5-16.5)
Mean change (primary analysis) <sup>a</sup>	15 <sup>b</sup>	8.9 ± 4.4	9.5 (0-16.5)

<sup>a</sup> p-value was <0.0001

<sup>b</sup> The mean change was set to 0 for 2 subjects with missing MCF data.

mm = millimeter

Adverse reactions encountered during the clinical trials are outlined under **ADVERSE EFFECTS**.

## **INDICATIONS**

Treatment of acute bleeding episodes in patients with congenital fibrinogen deficiency, including afibrinogenaemia and hypofibrinogenaemia.

There is limited experience with the use of the product for the treatment of congenital dysfibrinogenaemia (see **PRECAUTIONS**).

## **CONTRAINDICATIONS**

RiaSTAP<sup>®</sup> is contraindicated in individuals with a known hypersensitivity to any of the components of the product.

## **PRECAUTIONS**

### **Thrombosis**

There is a risk of thrombosis when patients with congenital fibrinogen deficiency are treated with human fibrinogen particularly with high dose or repeated dosing. Thrombosis may occur spontaneously in patients with congenital fibrinogen deficiency with or without the use of fibrinogen replacement therapy. Patients given human fibrinogen should be observed closely for signs or symptoms of thrombosis.

Some patients with congenital dysfibrinogenaemia may have an increased tendency to thrombosis. The use of RiaSTAP<sup>®</sup> in such patients should only be undertaken by haematologists experienced in the treatment of coagulation disorders.

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 RiaSTAP<sup>®</sup> should be weighed against the risk of thromboembolic complications. Caution and close monitoring should also be performed.

### **Allergic Reactions**

If allergic or anaphylactic-type reactions occur, the injection/infusion should be stopped immediately. In case of anaphylactic shock, standard medical treatment for shock should be implemented.

In the case of replacement therapy with coagulation factors in other congenital deficiencies, antibody reactions (including inhibitor information) have been observed, but there is currently no data with fibrinogen.

### **Sodium**

RiaSTAP<sup>®</sup> contains up to 164 mg (7.1 mmol) sodium per vial. This is to be taken into consideration by patients on a controlled sodium diet.

Refer to **DOSAGE AND ADMINISTRATION** section for further precautions regarding administration of RiaSTAP<sup>®</sup>.

### **Pathogen Safety**

This product is made from human plasma. Products made from human plasma may contain infectious agents such as viruses 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 infectious agents and by testing for the presence of certain viral markers. In addition, virus removal and inactivation procedures are included in the manufacturing process.

The measures taken are considered effective for enveloped viruses such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV), and for the non-enveloped virus hepatitis A 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). Despite these measures, such products may still potentially transmit disease. There is also the possibility that other known or unknown infectious agents may be present in such products.

Vaccination for patients in receipt of medicinal products from human plasma should be considered where appropriate.

### **Effects on fertility**

No studies examining the effect of RiaSTAP<sup>®</sup> on fertility have been conducted.

### **Use in pregnancy**

The safety of human fibrinogen for use in human pregnancy has not been established in controlled clinical trials. Clinical experience with human fibrinogen 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. RiaSTAP<sup>®</sup> should only be used during pregnancy if clearly indicated.

### **Use in lactation**

The safety of human fibrinogen for use during lactation has not been established in controlled clinical trials. RiaSTAP<sup>®</sup> should only be used during lactation if clearly indicated.

### **Paediatric use**

The efficacy and safety of RiaSTAP<sup>®</sup> in the paediatric population has not been established in controlled clinical trials.

### **Use in the elderly**

The efficacy and safety of RiaSTAP<sup>®</sup> in the elderly population has not been established in controlled clinical trials.

### **Carcinogenicity**

No carcinogenicity studies have been conducted with RiaSTAP<sup>®</sup>.

### **Genotoxicity**

No genotoxicity studies have been conducted with RiaSTAP<sup>®</sup>.

### **Interactions with other medicines**

The interaction of RiaSTAP<sup>®</sup> with other drugs has not been established in appropriate studies.

### **Effects on laboratory tests**

Human fibrinogen is an endogenous plasma protein so no specific effects on laboratory tests are anticipated.

## **ADVERSE EFFECTS**

The following adverse reactions have been reported from clinical studies and post-marketing experience as well as scientific literature. The following standard categories of frequency are used:

Very common:  $\geq$  1/10  
 Common:  $\geq$  1/100 and  $<$ 1/10  
 Uncommon:  $\geq$  1/1,000 and  $<$ 1/100  
 Rare:  $\geq$  1/10,000 and  $<$ 1/1,000  
 Very rare:  $<$  1/10,000 (including reported single cases)

System, Organ, Class (SOC)	Events	Frequency Category
Immune system disorders	Allergic-anaphylactic reactions (see footnote 1)	Rare
Vascular disorders	Thromboembolic episodes (see footnote 2)	Very rare
General disorders and administration site conditions	Increase in body temperature	Rare
Nervous System disorders	Headache	Rare

1. Allergic reactions include: generalised urticaria, rash, fall in blood pressure, dyspnoea
2. These episodes can include myocardial infarction and pulmonary embolism, deep vein thrombosis and arterial thrombosis

For safety with respect to transmissible agents, refer to the **Pathogen Safety** section.

## DOSAGE AND ADMINISTRATION

### Dosage

Treatment should be initiated under the supervision of a physician experienced in the treatment of coagulation disorders.

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.

Only general dosage guidelines are given below. Normal plasma fibrinogen level is in the range of 2.0 – 4.5 g/L. The critical plasma fibrinogen level below which haemorrhages may occur is approximately 1.0 g/L.

Clinical data on the use of RiaSTAP<sup>®</sup> in patients undergoing surgical procedures are very limited. In case of 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.

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

### Dosage for neonates, infants and children

Limited data from clinical studies regarding the dosage of RiaSTAP<sup>®</sup> 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.

### **Reconstitution**

The procedures below are provided as general guidelines for preparation and reconstitution of RiaSTAP<sup>®</sup>.

Use aseptic technique when preparing and reconstituting RiaSTAP<sup>®</sup>.

Reconstitute RiaSTAP<sup>®</sup> at room temperature as follows:

1. Remove the cap from the product vial to expose the central portion of the rubber stopper.
2. Clean the surface of the rubber stopper with an antiseptic solution and allow it to dry.
3. Using an appropriate transfer device or syringe, transfer 50 mL of Water for Injections into the product vial.
4. Gently swirl the product vial to ensure the product is fully dissolved. Do not shake the vial.

After reconstitution, the RiaSTAP<sup>®</sup> solution should be colourless and clear to slightly opalescent. Inspect visually for particulate matter and discoloration prior to administration. Do not use if the solution is cloudy or contains particulates.

### **Administration**

Do not mix RiaSTAP<sup>®</sup> with other medicinal products or intravenous solutions. RiaSTAP<sup>®</sup> should be administered through a separate injection site.

Use aseptic technique when administering RiaSTAP<sup>®</sup>.

Administer RiaSTAP<sup>®</sup> at room temperature by slow intravenous injection at a rate not exceeding 5 mL per minute.

It is strongly recommended that every time RiaSTAP<sup>®</sup> is administered to a patient, the name and batch number of the product are recorded in the patient notes in order to maintain a link between the patient and the batch of product.

**CAUTION: This product does not contain an antimicrobial preservative. To reduce microbiological hazard, the product should be used as soon as practicable after reconstitution. If it is not administered immediately, it must be stored below 25°C and used within 6 hours of reconstitution. The reconstituted solution should not be stored in the refrigerator. Any unused solution must be discarded appropriately. Use in one patient**

**on one occasion only.**

### **OVERDOSAGE**

In order to avoid overdosage, regular monitoring of the plasma level of fibrinogen during therapy is indicated.

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

### **PRESENTATION**

Each product package consists of one vial of RiaSTAP<sup>®</sup> containing nominally 1 g of freeze dried fibrinogen powder for reconstitution with 50 mL of Water for Injections (not provided).

### **STORAGE CONDITIONS**

Store below 25°C. Do not freeze. Protect from light. Do not use after the expiry date.

### **NAME AND ADDRESS OF THE SPONSOR AND DISTRIBUTOR**

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### **NAME AND ADDRESS OF THE MANUFACTURER**

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### **POISON SCHEDULE OF THE MEDICINE**

Unscheduled

Date of Therapeutic Goods Administration approval: 02 August 2010

<sup>®</sup> **Registered trademark of CSL Group of Companies**

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