

NEW ZEALAND DATA SHEET

1 PRODUCT NAME

RiaSTAP[®] 1 g, powder and diluent for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

RiaSTAP[®] is a sterile freeze-dried fibrinogen (coagulation factor I) concentrate derived from human plasma.

RiaSTAP[®] is presented as one vial of powder for injection containing 1 g of human fibrinogen and one vial of diluent containing 50 mL of Water for Injections (WFI). The reconstituted solution contains approximately 20 mg/mL of human fibrinogen.

Excipient with 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 and diluent for solution for injection

Powder: white

Diluent (WFI): clear, colourless.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Dose and method of administration

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

Dose

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.

NEW ZEALAND DATA SHEET

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[®] 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[®] 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

RiaSTAP[®] should be reconstituted according to section 6.6.

Do not mix RiaSTAP[®] with other medicinal products or intravenous solutions. RiaSTAP[®] should be administered through a separate injection site.

Use aseptic technique when administering RiaSTAP[®].

Administer RiaSTAP[®] at room temperature by slow intravenous injection at a rate not exceeding 5 mL per minute.

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.

NEW ZEALAND DATA SHEET

It is strongly recommended that every time RiaSTAP[®] 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.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

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 safety and efficacy of RiaSTAP[®] in the treatment of congenital dysfibrinogenaemia have not been established.

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 (TEE) or disseminated intravascular coagulation, the potential benefit of treatment with RiaSTAP[®] 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[®] 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 70mg/kg body weight is applied. This is to be taken into consideration by patients on a controlled sodium diet.

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, the RiaSTAP[®] manufacturing process

NEW ZEALAND DATA SHEET

includes pasteurisation at +60°C for 20 hours and multiple precipitation and absorption steps as dedicated virus removal and inactivation procedures to reduce the possibility of virus transmission. 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.

Paediatric population

The efficacy and safety of RiaSTAP[®] in the paediatric population has not been established in controlled clinical trials.

Elderly population

The efficacy and safety of RiaSTAP[®] in the elderly population has not been established in controlled clinical trials.

Effect on laboratory tests

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

4.5 Interaction with other medicines and other forms of interaction

No interaction studies have been performed.

4.6 Fertility, pregnancy and lactation

Fertility

There are no data available on fertility.

Pregnancy

Animal reproduction studies have not been conducted with RiaSTAP[®]. Since the active substance is of human origin, it is catabolised 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.

NEW ZEALAND DATA SHEET

The safety of human plasma fibrinogen products for use in human pregnancy has not been established in controlled clinical trials.

Clinical experience with fibrinogen products in the treatment of obstetric complications suggests that no harmful effects on the course of the pregnancy or health of the foetus or the neonate are to be expected.

Lactation

It is unknown whether RiaSTAP[®] is excreted in human milk. The safety of human plasma fibrinogen products for use during lactation has not been established in controlled 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.

4.7 Effects on ability to drive and use machines

RiaSTAP[®] has no influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

Allergic or anaphylactic type reactions have been uncommonly observed. The events reported in association with allergic/anaphylactic reactions include generalised urticarial, rash, dyspnoea, tachycardia, nausea, vomiting, chills, pyrexia, chest pain, cough, blood pressure decreased, and anaphylactic shock (see section 4.4).

The risk of TEE following the administration of fibrinogen concentrate (see section 4.4) as determined in clinical trials is further described in **Table 1**.

Pyrexia has been very commonly observed.

Tabulated list of adverse drug reactions (ADRs)

Table 1 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 clinical trials performed in aortic surgery with or without other surgical procedures according to the following convention: very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1000$); very rare ($< 1/10,000$) or unknown (cannot be estimated from the available data).

The calculated frequency is based on crude incidence rates without considering the frequency of the comparator arm. It should be noted that in the clinical trials included in the analysis, the incidence of TEEs was higher in the placebo arm. In view of the fact that these trials were conducted in only the narrow population of aortic surgery with or without other surgical procedures, adverse drug reaction

NEW ZEALAND DATA SHEET

rates observed in these trials may not reflect the rates observed in clinical practice and are unknown for clinical settings outside the studied indication.

Table 1: List of adverse drug reactions (ADRs)

MedDRA System, Organ, Class (SOC)	Undesirable effects	Frequency (In aortic surgery with or without other surgical procedures)
Immune system disorders	Allergic or anaphylactic reactions	Uncommon
Vascular disorders	Thromboembolic events*	Common**
General disorders and administration site conditions	Pyrexia	Very 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 compared with placebo.

Description of selected adverse reactions

The first study is a Phase II study of fibrinogen concentrate human (FCH) compared with placebo (saline) in subjects with acute bleeding while undergoing aortic repair surgery. The second study is a Phase III study of FCH versus placebo (saline) to control bleeding during complex cardiovascular surgery. In the first study (N = 61), TEE occurred similarly in fibrinogen and placebo groups. In the second study (N = 152), TEE occurred more frequently in the placebo group than in the FCH group (see **Table 2**).

Table 2: Pooled incidence rate of listed ADRs from company sponsored clinical trials

ADRs	FCH (N = 107)	Placebo (N = 106)
Pyrexia	11 (10.4%)	5 (4.7%)
Thromboembolic events	8 (7.4%)	11 (10.4%)
Allergic or anaphylactic reaction	1 (0.9%)	0

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

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions <https://nzphvc.otago.ac.nz/reporting/>.

4.9 Overdose

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

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

NEW ZEALAND DATA SHEET

For advice on the management of overdose please contact the National Poisons Centre on 0800 POISON (0800 764766).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihemorrhagics, human fibrinogen

ATC code: B02BB01

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.

Clinical efficacy and safety

The pharmacokinetic study (see section 5.2) evaluated the single-dose pharmacokinetics and maximum clot firmness (MCF) in subjects with afibrinogenemia. MCF was determined by thromboelastometry (ROTEM) testing. MCF was measured to demonstrate functional activity of replacement fibrinogen when a fixed dose of RiaSTAP[®] 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[®]. RiaSTAP[®] was found to be effective in increasing clot firmness in patients with congenital fibrinogen deficiency (afibrinogenemia) as measured by thromboelastometry. The study results demonstrated that the MCF values were significantly higher after administration of RiaSTAP[®] 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*.

NEW ZEALAND DATA SHEET

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) ^a	15 ^b	8.9±4.4	9.5 (0–16.5)

mm = millimeter.

^a p-value was <0.0001.

^b The mean change was set to 0 for 2 subjects with missing MCF data.

Adverse reactions encountered during the clinical trials are outlined in section 4.8.

5.2 Pharmacokinetic properties

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 4** provides the pharmacokinetic results.

NEW ZEALAND DATA SHEET

Table 4: Pharmacokinetic results for fibrinogen activity

Parameter (n = 14)	Mean±SD	Median (range)
t _{1/2} [h]	78.7±18.13	77.1 (55.73–117.26)
C _{max} [g/L]	1.4±0.27	1.3 (1.00–2.10)
AUC for dose of 70 mg/kg [h•mg/mL]	124.3±24.16	126.8 (81.73–156.40)
Extrapolated part of AUC [%]	8.4±1.72	7.8 (6.13–12.14)
Cl [mL/h/kg]	0.59±0.13	0.55 (0.45–0.86)
MRT [h]	92.8±20.11	85.9 (66.14–126.44)
V _{ss} [mL/kg]	52.7±7.48	52.7 (36.22–67.67)
IVR [mg/L per mg/kg body weight]	18±3.5	17 (13.0–27.3)

SD = standard deviation.

t_{1/2} = terminal elimination half-life.

h = hour.

C_{max} = maximum concentration within 4 hours.

AUC = area under the curve.

Cl = clearance.

MRT = mean residence time.

V_{ss} = volume of distribution at steady state.

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, carcinogenicity 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

Powder:

Albumin

Arginine hydrochloride

Sodium chloride

Sodium citrate

Sodium hydroxide (for pH adjustment)

Diluent:

Water for Injections

6.2 Incompatibilities

Do not mix RiaSTAP[®] with other medicinal products or intravenous solutions. RiaSTAP[®] should be administered through a separate injection site.

NEW ZEALAND DATA SHEET

6.3 Shelf life

5 years

Reconstituted product

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.

6.4 Special precautions for storage

Store at 2°C to 8°C (Refrigerate. Do not freeze). Protect from light. Do not use after the expiry date.

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

6.5 Nature and contents of container and special equipment for use

Each pack contains:

- One glass vial of RiaSTAP® 1g human fibrinogen, with a rubber stopper closed with an aluminium cap and plastic disc
- One glass vial of 50 mL Water for Injections, with a rubber stopper closed with an aluminium cap and a plastic disc
- One transfer set.

RiaSTAP® is packaged in latex-free materials.

6.6 Special precautions for disposal and other handling

Reconstitution

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

Use aseptic technique when preparing and reconstituting RiaSTAP®.

Warm both the Water for Injections and RiaSTAP® in unopened vials to room or body temperature (not above 37°C).

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 the provided transfer set, transfer 50 mL of Water for Injections into the product vial.
4. Gently swirl the product vial to ensure the product is fully dissolved.
 - Avoid shaking which causes formation of foam.
 - The powder should be completely reconstituted within 15 minutes (generally 5 to 10 minutes).

NEW ZEALAND DATA SHEET

After reconstitution, the RiaSTAP[®] 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.

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

7 MEDICINE SCHEDULE

General Sale Medicine

8 SPONSOR

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2 December 2019

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NEW ZEALAND DATA SHEET

SUMMARY TABLE OF CHANGES

Section changes	Summary
5.1	Information about provisional consent removed