AUSTRALIAN PRODUCT INFORMATION

Biostate®

(Human coagulation factor VIII and human von Willebrand factor complex)

Powder and diluent for solution for injection

1 NAME OF THE MEDICINE

Human coagulation factor VIII and human von Willebrand factor complex.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Biostate® is a high purity, sterile, powder for injection containing a human coagulation factor VIII (FVIII) and human von Willebrand factor (VWF) complex. Biostate® is manufactured from human plasma collected by Australian Red Cross Lifeblood. The FVIII/VWF complex in Biostate® is purified from cryoprecipitate using selective precipitation and size exclusion chromatography steps.

Von Willebrand Factor (VWF)

Following reconstitution, 1 mL of Biostate® contains:

- Biostate® 50 IU FVIII/mL: approximately 120 IU of human plasma derived VWF
- Biostate® 100 IU FVIII/mL: approximately 240 IU of human plasma derived VWF.

The VWF activity of Biostate® is determined using a VWF to platelet glycoprotein Ib binding activity assay (VWF:Ac). The VWF activity is expressed as international units (IU) and 1 IU VWF:Ac is equivalent to 1 IU VWF ristocetin cofactor (VWF:RCo) in accordance with the WHO standard. The specific VWF activity of the product prior to the addition of human albumin as a stabiliser is approximately 100 IU of VWF/mg protein.

Factor VIII (FVIII)

Following reconstitution, 1 mL of Biostate® contains:

- Biostate® 50 IU FVIII/mL: approximately 50 IU of human plasma-derived coagulation FVIII
- Biostate® 100 IU FVIII/mL: approximately 100 IU of human plasma-derived coagulation FVIII.

The FVIII potency (IU) is determined using the European Pharmacopoeia chromogenic assay. The activity of FVIII is measured as FVIII coagulation activity (FVIII:C). The specific FVIII activity of Biostate® prior to the addition of human albumin as a stabiliser is approximately 50 IU of FVIII/mg protein.

Biostate® contains other proteins such as fibrinogen, fibronectin, immunoglobulins (IgA, IgM, IgG) and transforming growth factor-β (TGF-β), all of which are present at significantly lower levels than in normal plasma.

Biostate® is available in two different concentrations (strengths) and in four different presentations as detailed in **Table 1**. The amount of VWF in the final product is dependent on the method of preparation of the cryoprecipitate, and this influences the VWF:FVIII ratio. Biostate® contains VWF and FVIII in a ratio of 2.4:1.

Table 1: Biostate® presentations[a]

Concentration	**50 IU FVIII/mL / 120 IU VWF/mL**		**100 IU FVIII/mL / 240 IU VWF/mL**	
Presentation	**250 IU FVIII/ 600 IU VWF**	**500 IU FVIII/ 1200 IU VWF**	**500 IU FVIII/ 1200 IU VWF**	**1000 IU FVIII/ 2400 IU VWF**
Active ingredients (IU/vial)				
FVIII:C	250	500	500	1000
VWF:Ac	600	1200	1200	2400
Reconstitution volume (mL)	**5**	**10**	**5**	**10**

[a] Nominal values.
FVIII:C – FVIII coagulation activity.
VWF:Ac – VWF to platelet glycoprotein Ib binding activity, equivalent to VWF:RCo.
Note: Not all registered presentations may be supplied.

For the full list of excipients, see section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Powder and diluent for solution for injection

Powder: white or pale yellow

Diluent: clear, colourless (WFI)

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Biostate® is indicated for:

- the prophylaxis and treatment of non-surgical and surgical bleeding in patients with von Willebrand disease when desmopressin (DDAVP) treatment is ineffective or contraindicated.
- the prophylaxis and treatment of non-surgical and surgical bleeding associated with FVIII deficiency due to haemophilia A.

4.2 DOSE AND METHOD OF ADMINISTRATION

Dosage

It is recommended that prescribed doses of Biostate® should be expressed as International Units written in full.

The dosage recommendations provided are general guidelines for therapy. The exact loading and maintenance doses and dosing intervals should be based on the patient's clinical condition and response to therapy. Laboratory tests should be performed to ensure that the desired plasma FVIII and VWF concentrations are achieved.

The active ingredients, VWF and FVIII are present in a ratio of 2.4:1.

Von Willebrand disease population

Provided in **Table 2** are VWD dosage guidelines for patients with severe VWD (<10% normal VWF). In patients with less severe VWF deficiency, doses may need to be adjusted down to achieve the desired serum plasma concentrations. It is recommended that plasma VWF and FVIII concentrations are determined at suitable time intervals.

Table 2: VWD dosage guidelines

Indication	Dose (IU/kg)		Dose frequency	Target FVIII/VWF (%) (IU/dL)
	FVIII:C	VWF:Ac[1]		
Spontaneous bleeding episodes	10–20	25–50	Initial	VWF peak level >50%, FVIII >30%
	10	25	Subsequent every 12–24 hours	VWF/FVIII trough levels of >30% until bleeding stops (usually 2–4 days)
Minor surgery	25	60	Daily	VWF/FVIII trough levels of >30% until healing is complete (usually 2–4 days)
Major surgery	25–35	60–80	Initial	VWF peak level >100%, FVIII >60%
	15–25	30–60	Subsequent every 12–24 hours	VWF/FVIII trough levels of >50% until healing is complete (usually 5–10 days)
Prophylaxis	10–15	25–40	1–3 times weekly	Trough >1

[1] Equivalent to VWF:RCo.

In young patients or patients with gastrointestinal bleeds or menorrhagia, shorter dose intervals or higher doses may be necessary. The clinical status of the individual patient, as well as their VWF:RCo and FVIII:C plasma levels, should be taken into consideration in determining the dose and duration of treatment.

Paediatric VWD population

Based on results from a clinical trial in paediatric patients under 12 years of age to achieve haemostasis, a prophylactic dose range of 40–80 IU VWF:Ac/kg body weight (equivalent to VWF:RCo) 1 to 3 times a week should be considered.

Haemophilia A population

Provided in **Table 3** are dosage guidelines for patients with Haemophilia A.

Table 3: Haemophilia A dosage guidelines

Indication	Dose (IU/kg)	Dose frequency	Treatment day(s) or duration	Target FVIII (%) (IU/dL)	
Minor bleeding episodes	10–15	12–24 hourly	1–2	Peak	20–30
Moderate to severe bleeding episodes e.g. haemarthroses	15–40	8–24 hourly	1–4	Peak	30–80
Life threatening bleeding e.g. intracranial haemorrhage	50–60 20–25	Single dose 8–12 hourly	1 2–10	Peak Trough	>100 80–100
Minor surgery	20–30 20–25 20–30	Single dose 12 hourly 24 hourly	Pre-op 1–3 ≥4	Peak Trough Trough	40–60 40–50 20–30
Major surgery	40–50 20–25 15–20 10–20	Single dose 8–12 hourly 8–12 hourly 12 hourly	Pre-op 1–3 4–6 ≥7	Peak Trough Trough Trough	80–100 80–100 60–80 40–60
Dentistry e.g. invasive dental procedures, extractions, surgery	35–40 25–30	Single dose 12 hourly	Pre-op 1–3	Peak Trough	70–80 50–60
Prophylaxis	25–40	3 times weekly	Ongoing	Trough	1

Note: The 'pre-op' dose is the loading dose prior to surgery, day 1 is the day of surgery and trough levels need to be maintained above target on day of surgery, and subsequently. For extensive dental clearance or surgery, higher levels may be necessary for longer periods of time. The use of an antifibrinolytic agent in support of factor replacement is strongly recommended after dental extractions.

Paediatric haemophilia A population

Dosing in haemophilia A in children (<12 years of age) and adolescents (12 to <18 years of age) is based on body weight and is therefore generally based on the same guidelines as for adults. In some cases shorter dose intervals or higher doses may be necessary. The frequency of administration should always be oriented to the clinical effectiveness in the individual case.

Continuous infusion

Studies using continuous infusion have not been carried out in patients. However, it is suggested that this method is suitable for covering surgical procedures. The product required should be reconstituted to the same volume and in the same diluent as for bolus infusion, and administered using an infusion pump suitable for this volume. Reconstitution should be done under aseptic conditions, and sterile integrity of the delivery device should be maintained.

Monitoring advice

It is recommended that plasma FVIII:C and/or VWF:RCo concentrations be determined in patient's plasma at suitable intervals and during the treatment of severe bleeding episodes.

Reconstitution

1. Ensure that the Biostate® and Water for Injections vials are at room temperature (20°C to 30°C). Remove the flip-top caps from the Biostate® and Water for Injections vials. Apply an appropriate disinfectant to both rubber stoppers and allow to dry. Remove the lid of the Mix2Vial™ packaging. If the seal of the lid is not intact or there are any concerns about the integrity of the Mix2Vial™, do not use it but return it to Australian Red Cross Lifeblood.
2. Place the Water for Injections vial upright on a level surface. Pick up the Mix2Vial™ in its outer package and invert it. Holding the Water for Injections vial securely, push the blue end of the Mix2Vial™ vertically down through the Water for Injections vial stopper.
3. Carefully remove the Mix2Vial™ outer package. Ensure the Mix2Vial™ remains attached to the Water for Injections vial.
4. Place the Product vial upright on a level surface, invert the Water for Injections vial with the Mix2Vial™ attached. Holding the Product vial securely push the clear end of the Mix2Vial™ vertically down through the Product vial stopper. The Water for Injections will be drawn out of its vial and into the Product vial by the vacuum within the Product vial. In the unlikely event that the vial does not contain a vacuum, do not use the product, but return it to Australian Red Cross Lifeblood.
5. Leaving the system connected, gently swirl to ensure that the product is fully dissolved. Unscrew the Mix2Vial™ into two separate pieces. Discard the Water for Injections vial and the blue end of the Mix2Vial™.
6. Keeping the Product vial upright, attach the syringe to the clear end of the Mix2Vial™. Invert the system and draw the reconstituted product into the syringe. When the product has been transferred, discard the Mix2Vial™ and Product vial.

Note: The Mix2Vial™ is intended to filter the contents of a single vial of Biostate® only. If multiple vials of Biostate® are to be administered, a separate Mix2Vial™ must be used for each vial.

Do not refrigerate Biostate® once it has been reconstituted.

Biostate® is a white or pale yellow powder contained in a glass vial. Upon reconstitution it forms a colourless to slightly yellow solution with a clear to opalescent appearance. After filtering/withdrawal, the reconstituted product should be inspected visually for particulate matter and discolouration prior to administration. Do not use visibly cloudy solutions or solutions still containing flakes or particles. If a clot or gel forms, do not use the product but return it to Australian Red Cross Lifeblood.

NOTE: Whilst the physico-chemical stability of the active ingredients has been demonstrated for 8 hours following reconstitution at room temperature (below 25°C), Biostate® does not contain an antimicrobial preservative. Therefore, it is recommended that the reconstituted product should be used as soon as practicable.

Use in one patient on one occasion only.

Administration

Biostate® is intended for intravenous administration.

1. With the Biostate® vial upright, attach a plastic disposable syringe to the Mix2Vial™ (transparent plastic part). Invert the system and draw the reconstituted Biostate® into the syringe by pulling the plunger back slowly. One large syringe may be used to pool several vials of reconstituted Biostate®.
2. Once the Biostate® has been transferred into the syringe, firmly hold the barrel of the syringe (keeping the syringe plunger facing down) and detach the Mix2Vial™ from the syringe. Discard the Mix2Vial™ (transparent plastic part) and empty Biostate® vial in an appropriate waste container. Fit the syringe to a suitable injection needle to administer the reconstituted Biostate®. Do not use the Mix2Vial™ for injection.
3. Give the dose slowly by the intravenous route (usually within 5 to 6 minutes, or as tolerated by the patient). The injection/infusion rate should not exceed 6 mL per minute and the patient should be observed carefully during administration. If there is any reaction that might be related to the administration of Biostate®, the rate of injection should be decreased or if needed, the application should be stopped (see section 4.4 Special warnings and precautions for use).

4. When the contents of more than one vial are to be given, it will be convenient to pool the total amount prior to administration (e.g. in a large syringe or sterile bag). This must be done aseptically.
5. To reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. For use in surgery, the conditions described under **Continuous infusion** can apply. This product is for single use only and any unused portion remaining in the vial must be discarded appropriately.
6. The solution must not be added or mixed with any other fluids to be given, including whole blood.

Medical personnel, family carers and patients should be adequately trained in the techniques for the preparation and the administration of Biostate®. A detailed and comprehensive Consumer Medicine Information document is available but this instruction must not take the place of professional medical advice and supervised training in the administration of Biostate®.

Spillage and breakages

Should a break in the container or spillage occur, due precautions should be taken to avoid contamination of cuts and abrasions, as well as to avoid inhalation or swallowing of the spillage. Adequate disinfection can be obtained with the application of 1% sodium hypochlorite for 15 minutes. Commercial bleaches may be diluted appropriately to obtain this concentration.

4.3 CONTRAINDICATIONS

Biostate® is contraindicated in individuals with a history of anaphylactic or severe systemic response to coagulation FVIII and/or VWF preparations. Also it is contraindicated in individuals with a known hypersensitivity to any of the product components.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity

Allergic type hypersensitivity reactions are possible. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of the medicinal product immediately and contact their physician. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension and anaphylaxis. In case of shock, the current medical standards for shock treatment should be observed.

Haemophilia A

Inhibitors

The formation of neutralising antibodies (inhibitors) to FVIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against the FVIII procoagulant activity, which are quantified in Bethesda Units (BU) per mL of plasma, using appropriate biological testing. The risk of developing inhibitors is correlated to the exposure to anti-haemophilic FVIII, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days.

Cases of recurrent inhibitor (low titre) have been observed after switching from one FVIII product to another in previously treated patients with more than 100 exposure days who have a previous history of inhibitor development. Therefore, it is recommended to monitor patients carefully for inhibitor occurrence following any product switch.

In general, all patients treated with coagulation FVIII products should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. If the expected FVIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for FVIII inhibitor presence should be performed. In patients with high levels of inhibitor, FVIII therapy may not be effective and other therapeutic options should be considered. The management of such patients should be directed by physicians with experience in the care of haemophilia A patients and those with FVIII inhibitors.

Von Willebrand disease

There is a risk of occurrence of thrombotic events, particularly in patients with known clinical or laboratory risk factors. Therefore, patients at risk must be monitored for early signs of thrombosis. Prophylaxis against venous thromboembolism should be instituted for patients at risk according to the current medical standards.

When using a FVIII-containing VWF product, continued treatment may cause an excessive rise in FVIII:C. In patients receiving FVIII-containing VWF products, plasma levels of FVIII:C should be monitored to avoid sustained excessive FVIII:C plasma levels which may increase the risk of thrombotic events, and antithrombotic measures should be considered.

Patients with VWD, especially type 3 patients, may develop neutralising antibodies (inhibitors) to VWF. If the expected VWF:RCo activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, an appropriate assay should be performed to determine if a VWF inhibitor is present. In patients with high levels of inhibitor, therapy may not only be ineffective but also lead to anaphylactoid reactions and other therapeutic options should be considered.

Pathogen safety

This product is made from human plasma. Products made from human plasma may contain infectious agents, such as viruses and theoretically Creutzfeldt Jakob Disease (CJD) agents that can cause disease.

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses.

The manufacturing process includes solvent detergent (tri-n-butyl phosphate and polysorbate 80) and dry heat treatment (80°C for 72 hours) as dedicated virus inactivation steps to reduce the theoretical risk of virus transmission. The solvent detergent, dry heat treatment, and partitioning steps used in the manufacture of Biostate® have been demonstrated to be effective virus inactivation/removal steps *in vitro* for the relevant viruses, human immunodeficiency virus (HIV) and hepatitis A virus (HAV), and also with models for hepatitis B virus (HBV) and hepatitis C virus (HCV). The manufacturing process also contributes to inactivation/removal of human parvovirus B19 (B19).

Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens.

The measures taken are considered effective for enveloped viruses such as HIV, HBV and HCV, and for the non-enveloped virus HAV. The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19.

Parvovirus B19 infection may be serious for pregnant women and for individuals with immunodeficiency or increased erythropoiesis.

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

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

Use in the elderly

The safety of this product for use in the elderly population has not been established in appropriate studies.

Paediatric use

The listed warnings and precautions apply both to adults and paediatrics.

Effects on laboratory tests

FVIII and/or VWF are endogenous plasma proteins therefore no specific effects on laboratory tests are anticipated.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Interaction of VWF and FVIII with other medicinal products has not been studied.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

Animal reproduction studies have not been conducted with Biostate®.

Use in pregnancy and lactation

Von Willebrand disease

Experience in the treatment of pregnant or breast-feeding women is not available. Biostate® should be administered to pregnant or breast-feeding VWF deficient women only if clearly indicated, taking into consideration that delivery confers an increased risk of haemorrhagic events in these patients.

Haemophilia A

Based on the rare occurrence of haemophilia A in women, experience regarding the treatment during pregnancy and breast-feeding is not available.

Therefore, Biostate® should be used during pregnancy and breast-feeding only if clearly indicated.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No effects on ability to drive and use machines have been observed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The adverse reactions presented in **Table 4** are based on experience from clinical trials and postmarketing experience from patients with haemophilia A and VWD.

The following standard categories of frequency are used where data are available:

Very common	≥	1/10
Common	≥	1/100 and <1/10
Uncommon	≥	1/1000 and <1/100
Rare	≥	1/10,000 and <1/1000
Very rare	<	1/10,000
Not known	frequency cannot be estimated from the available data.	

Table 4: Frequency of adverse reactions

MedDRA SOC	Adverse reaction*	Frequency in clinical trials	Frequency in postmarketing surveillance
Blood and lymphatic system disorders	FVIII inhibition	Common	Very rare
	VWF inhibition	Not known**	Very rare
Immune system disorders	Hypersensitivity (including tachycardia, chest pain, chest discomfort and back pain)	Common	Very rare
Investigations	Liver function test abnormal	Uncommon	Very rare
Nervous system disorders	Dysgeusia	Uncommon	Very rare
Vascular disorders	Thromboembolic event	Uncommon	Very rare
General disorders and administration site conditions	Pyrexia	Common	Very rare
	Headache	Very common	Very rare

* Adverse events adjudicated as related to Biostate®.

** Observed during postmarketing surveillance, not observed in clinical trials.

Description of selected adverse reactions

FVIII inhibition: Patients with haemophilia A may develop neutralising antibodies (inhibitors) to FVIII. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response.

VWF inhibition: Patients with VWD, especially type 3 patients, may develop neutralising antibodies (inhibitors) to VWF. If such inhibitors occur, the condition will manifest itself as an inadequate clinical response. Such antibodies are precipitating and may occur concomitantly to anaphylactic reactions. Therefore, patients experiencing an anaphylactic reaction should be evaluated for the presence of an inhibitor.

Hypersensitivity (allergic reactions): Includes angioedema, burning and stinging at the infusion site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy,

nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing have been observed on occasion, and may in some cases progress to severe anaphylaxis (including shock).

Thromboembolic events: In patients with VWD, there is a risk of occurrence of thromboembolic events, particularly in patients with known clinical or laboratory risk factors. In patients receiving FVIII-containing VWF products, sustained excessive FVIII:C plasma levels may increase the risk of thromboembolic events.

For safety with respect to transmissible agents, see section 4.4 Special warnings and precautions for use.

Paediatric population

Frequency, type and severity of adverse reactions in the Haemophilia A paediatric population is expected to be the same as in that observed in the adult population.

Frequency, type and severity of adverse reactions in the von Willebrand paediatric population is expected to be the same as in that observed in the adult population.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

Cases of overdose (twice the amount of the recommended dose) have been observed in clinical trials. No severe adverse reactions were associated with these cases. The risk of thromboembolic events cannot be excluded in case of major overdose, especially in patients with VWD.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

The Biostate® FVIII/VWF complex consists of two different non-covalently bound proteins: FVIII and VWF. FVIII is an essential cofactor in activation of factor X leading ultimately to the formation of thrombin and fibrin. VWF promotes platelet aggregation and platelet

adhesion on damaged vascular endothelium; it also serves as a stabilising carrier protein for the procoagulant protein FVIII.

Von Willebrand Disease (VWD) is an autosomally-inherited congenital bleeding disorder in which there is a deficiency or dysfunction of VWF. A reduction in VWF concentration in the bloodstream results in low FVIII activity and abnormal platelet function, which may result in excessive bleeding. The VWF activity in Biostate® exists in a 2.4:1 ratio with FVIII:C activity. Biostate® has been demonstrated to contain the high molecular weight (HMW) multimers of VWF. HMW multimers are considered to be important for correcting the haemostatic defect in patients with VWD as they are important for platelet adhesion.

Haemophilia A is an X-linked recessive blood coagulation disorder. It is caused by reduced FVIII activity, through either insufficient or abnormal synthesis of the FVIII protein, which is required for the formation of blood clots. Activated FVIII acts as a cofactor for activated factor IX, accelerating the conversion of factor X to activated factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed.

Clinical trials

A total of 221 subjects were exposed in the prospective clinical studies, including 147 subjects with haemophilia A and 74 subjects with VWD. Among these exposed subjects, 5 subjects with haemophilia A and 3 subjects with VWD were adolescents, (aged 12 to <18 years), 36 subjects with haemophilia A (1 with high titre FVIII inhibitors was <1 year old) and 18 subjects with VWD were paediatrics aged <12 years.

In addition, efficacy and safety data in VWD subjects were collected in 2 published investigator-led studies that included 43 adult VWD subjects (Shortt 2007) and 43 adolescents and children (Howman 2011). Fifteen paediatric haemophilia A subjects, with FVIII inhibitors, treated for immune tolerance induction are reported in a published investigator-led retrospective chart review (Robertson 2014).

Von Willebrand Disease

Efficacy in the control of non-surgical and surgical bleeding was assessed in 3 open-label non-controlled trials. A 4-point rating scale was used in all trials: None – no control of bleeding; Moderate – moderate control of bleeding, other treatment also required; Good – slight oozing, partial but adequate control of bleeding; Excellent – haemostasis achieved.

In the first trial, with a focus on non-surgical bleeds (NSB), the haemostatic efficacy for 98.2% of 407 evaluable NSB were assessed by the investigator as excellent or good and 1.7% as moderate. During the study 8 subjects experienced 125 major NSBs, of which 7 were mucosal bleeds. The investigator's overall assessment was excellent for 1 and moderate for

the other 6 major mucosal bleeds which were uterine bleeds; although for 4 of the later 6 bleeds the investigator had assessed efficacy as good on at least 1 day. Eight subjects in this trial were treated on-demand for 12 months before being switched to a prophylaxis regimen. The total number of NSB events decreased from 306 (ranging from 18 to 82 per subject, on-demand) to 10 in 5 of the subjects during prophylaxis. The haemostatic efficacy of all events treated with Biostate® was assessed by the investigator as excellent.

In the second trial the focus was on surgery. In 9 subjects undergoing 10 major surgical procedures, the efficacy was excellent or good in 10 (100%). In 11 patients undergoing 15 minor surgical procedures, haemostatic efficacy was excellent in 14 (93%) and good in 1 (7%). The mean dose to achieve haemostasis was 27 IU FVIII:C/kg/day for a median 2 days in non-surgical bleeding, 33 IU FVIII:C/kg/day for a median 2 days in minor surgery and 41 IU FVIII:C/kg/day for a median 7.5 days in major surgery.

In the third trial 12 paediatric subjects treated on-demand experienced 96 NSB events which included 26 major events, 13 of which were mucosal bleeds. Haemostatic efficacy was assessed as excellent (45%) and good (55%) by the investigator for all of the NSB events evaluated. Three subjects in this group underwent 8 minor surgical procedures (all were dental). For a group of 4 paediatric subjects receiving prophylaxis treatment, 73 NSB events required treatment, however the haemostatic efficacy for these events was assessed by the investigator as excellent for 81% and good for the remaining 19% of events.

In a retrospective review of surgical bleeding in 43 adult patients undergoing 58 procedures, the haemostatic efficacy was excellent or good in 100% of procedures. Efficacy in the VWD Type 3 patients (n=5) was rated as excellent in 55%. The mean dose to achieve haemostasis was 29 IU FVIII:C/kg/day for a mean 2 days (range 1–4) in minor dental procedures and 5 days (range 1–13) in major surgery. There was some concomitant use of tranexamic acid and desmopressin.

In a second retrospective review in children and adolescents, 42 surgical events were treated: 10 major events in 10 subjects and 32 minor surgical events in 21 subjects. Four episodes of post-surgical bleeding events were also treated in 4 subjects, who had not received the product to prevent bleeding during the procedure. A total of 72 NSB events were treated: 46 mucocutaneous in 11 subjects and 26 musculoskeletal or soft tissue bleedings in 13 subjects. Only tranexamic acid was used as an adjunctive therapy in these subjects.

The haemostatic efficacy for all surgical events was excellent or good in approximately 90% of events (90% major and 91% of minor surgical events). Haemostatic efficacy for all NSB events was rated as excellent or good in 94% of events, and within Type 3 VWD subjects in 98% of NSB events.

The mean daily dose was 51 IU FVIII/kg (range 13–151) for major surgery with a median treatment duration of 7 days (range 1–24) and 45 IU FVIII/kg (range 14–76) for minor surgery with a median treatment duration of 3 days (range 1–8). For NSB events, the mean daily dose was 45 IU FVIII/kg (range 16–192) with a median treatment duration of 1 day (range 1–13).

Efficacy and safety in acquired VWD has not been established.

Adverse reactions encountered during the clinical trials in VWD patients are included under section 4.8 Adverse effects (undesirable effects).

Haemophilia A

Efficacy in haemophilia A was assessed in 2 open-label, non-controlled trials.

In the first study in adult and adolescent subjects with haemophilia A, 81 subjects were treated with 77 subjects completing 6 months of treatment. Patients were treated either on-demand (including the prevention of bleeding in relation to surgery) or as prophylaxis. Of 656 evaluable bleeding events, 96.4% were assessed as excellent or good, 3.5% as moderate and 0.2% as none (one event, no efficacy).

During the study, a total of 37 surgical events occurred in 20 subjects; 12 events were major and 25 minor. Investigator's assessment of haemostatic efficacy at discharge was reported as excellent for 8 major and 10 minor surgical events, and as good for 2 major surgical events.

In the second study in paediatric subjects <12 years of age, 35 subjects were treated either on-demand or as prophylaxis, with 21 subjects completing at least 50 exposure days. In the on-demand group, all 318 evaluable bleeding events were assessed as excellent or good (24.2 and 75.8% respectively), including 98 (30.6%) major bleeds, 7 of which were mucosal. In the prophylaxis group 99.4% of the evaluable bleeding events (172) were assessed as excellent or good (1 event was moderate). Of the 85 major bleeding events (49.1%), none were mucosal. Five subjects in the prophylaxis group did not experience any bleeding event during treatment.

A total of 5 surgeries, 2 major and 3 minor, occurred during the study. The investigator's assessment of these events was reported as excellent for 2 (minor) surgeries and good for the remaining 3 surgeries.

The retrospective chart review of haemophilia A subjects with FVIII inhibitors describes exposure to high doses of Biostate®.

Adverse reactions encountered during the clinical trials in haemophilia A patients are included under section 4.8 Adverse effects (undesirable effects).

Efficacy and safety have not been studied in previously untreated patients.

5.2 PHARMACOKINETIC PROPERTIES

Von Willebrand Factor

The pharmacokinetics (PK) of the product have been evaluated in VWD patients in the non-bleeding state.

Based on a PK study with 12 subjects with VWD, the PK characteristics for VWF:RCo, VWF antigen (VWF:Ag) and VWF collagen binding (VWF:CB) in **Table 5** were observed following a single intravenous infusion of 80 IU VWF:RCo/kg.

Table 5: Pharmacokinetics data for VWF:RCo, VWF:Ag and VWF:CB

Parameter	VWF:RCo				VWF:Ag				VWF:CB			
	N	Mean	SD	Range	N	Mean	SD	Range	N	Mean	SD	Range
Incremental recovery (kg/mL)	12	0.017	0.002	0.01–0.02	12	0.018	0.002	0.01–0.02	12	0.020	0.004	0.02–0.02
Half-life (h)	8	13.7	9.2	6.1–35.1	12	18.3	4.0	11.4–27.0	12	16.0	4.6	9.4–25.1
$AUC_{0–72}$ (h.IU/mL)	12	17.7	9.7	8.6–38.0	12	37.8	13.3	22.6–64.7	12	24.8	8.8	14.8–41.1
MRT (h)	8	14.0	5.0	8.6–25.5	12	23.6	5.0	15.3–33.6	12	20.0	4.4	11.6–28.6
C_{max} (IU/mL)	12	1.65	0.63	0.93–3.36	12	2.29	0.59	1.52–3.66	12	1.68	0.50	1.04–2.66
T_{max} (h)	12	0.25[a]	–	0.25–1.03	12	0.25[a]	–	0.25–1.00	12	0.25[a]	–	0.25–1.00
C_{min} (IU/mL)	12	0.01	0.01	0.00–0.03	12	0.10	0.05	0.02–0.17	12	0.05	0.02	0.02–0.09
Total clearance (mL/(h.kg))	12	6.09	1.66	3.06–9.32	12	3.57	0.69	2.61–4.78	12	3.53	0.89	2.32–4.77
V_{ss} (mL/kg)	8	74.8	35.3	44.7–158.0	12	82.8	18.6	64.5–128.4	12	68.6	15.7	47.5–93.7

[a] median.

AUC = area under the curve; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; IU = International Unit; MRT = mean residence time; N = number of subjects; SD = standard deviation; T_{max} = time to maximum concentration; V_{ss} = volume of distribution at steady state; VWF:Ag = von Willebrand factor: antigen; VWF:CB = von Willebrand factor: collagen binding; VWF:RCo = von Willebrand factor: ristocetin cofactor.

Peak plasma levels of VWF usually occur within a mean time of 18 minutes (median 15 minutes) after injection.

Similar results for both VWF and FVIII PK parameters were found when assessed after 6 months of treatment.

A population PK analysis which included PK data from both the adult subjects and a trial in paediatric subjects, indicated that dosing both populations on a 80 IU/kg basis provides

similar concentrations for each of the VWF markers measured and found only body weight influences the PK of Biostate® which supports the dosing of Biostate® on an IU/kg basis.

Factor VIII

The pharmacokinetics of the product have been evaluated in haemophilia A patients in the non-bleeding state.

Based on a PK study with 16 subjects with haemophilia A, the PK characteristics for FVIII:C in **Table 6** were observed following a single intravenous infusion of 50 IU/kg.

Table 6: Pharmacokinetics data for FVIII:C

Parameter	FVIII:C			
	N	Mean	SD	Range
Incremental recovery (kg/mL)	16	0.021	0.006	0.011–0.032
Half-life (h)	16	13.40	2.53	8.78–18.51
AUC_{0-48} (h.IU/mL)	16	13.79	3.79	7.04–21.79
MRT (h)	16	16.96	3.68	11.29–26.31
C_{max} (IU/mL)	16	1.07	0.28	0.57–1.57
T_{max} (h)	16	0.81	0.94	0.42–4.03
C_{min} (IU/mL)	16	0.060	0.028	0.021–0.111
Total clearance (mL/(h.kg))	16	3.92	1.22	2.30–7.11
V_{ss} (mL/kg)	16	65.33	20.65	35.07–113.06

AUC = area under the curve; C_{max} = maximum plasma concentration; C_{min} = minimum plasma concentration; IU = International Unit; MRT = mean residence time; N = number of subjects; SD = standard deviation; T_{max} = time to maximum concentration; V_{ss} = volume of distribution at steady state; FVIII:C = factor VIII: coagulation activity.

Peak plasma levels of FVIII usually occur within a mean time of 49 minutes (median 30 minutes) after injection.

Similar PK results, including FVIII half-life, were found when PK parameters were assessed 6 months after the initial PK study. VWF PK parameters were not measured in the initial assessment or the repeat assessment after 6 months.

Paediatric population

There were small differences in PK parameters, reduced exposure and increased clearance, observed between the paediatric age groups (<6 years and 6–12 years) in both VWD and haemophilia A studies. The differences when compared with inherent subject variability are not expected to be clinically important.

The PK data in paediatric subjects are comparable to those observed in adult subjects.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

No genotoxicity studies have been conducted with Biostate®.

Carcinogenicity

No carcinogenicity studies have been conducted with Biostate®.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Human plasma proteins
Albumin stabiliser
Sucrose
Sodium citrate dihydrate
Sodium chloride
Trometamol
Calcium chloride dihydrate

6.2 INCOMPATIBILITIES

Compatibility studies have not been conducted, therefore Biostate® must not be mixed with other medicinal products.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the carton packaging.

Reconstituted product

Whilst the physico-chemical stability of the active ingredients has been demonstrated for 8 hours following reconstitution at room temperature (below 25°C), Biostate® does not contain an antimicrobial preservative. Therefore, it is recommended that the reconstituted product should be used as soon as practicable.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store at 2°C to 8°C (Refrigerate. Do not freeze). Biostate® can be stored below 25°C for a single period of 6 months. The product must not be returned to refrigeration after storage below 25°C. Protect from light. Do not use after the expiry date.

6.5 NATURE AND CONTENTS OF CONTAINER

Each presentation includes Biostate® powder for injection and WFI in clear glass vials with latex free rubber closures closed with an aluminium seal and a plastic flip-top cap.

Each presentation is supplied with a Mix2Vial™ filter transfer set.

- 250 IU FVIII/600 IU VWF vial of Biostate® (50 IU FVIII/mL, 120 IU VWF/mL), 5 mL vial of Water for Injections
- 500 IU FVIII/1200 IU VWF vial of Biostate® (50 IU FVIII/mL, 120 IU VWF/mL), 10 mL vial of Water for Injections
- 500 IU FVIII/1200 IU VWF vial of Biostate® (100 IU FVIII/mL, 240 IU VWF/mL), 5 mL vial of Water for Injections
- 1000 IU FVIII/2400 IU VWF vial of Biostate® (100 IU FVIII/mL, 240 IU VWF/mL), 10 mL vial of Water for Injections.

Not all registered presentations may be supplied.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

CAS number: 9001-27-8

7 MEDICINE SCHEDULE (POISONS STANDARD)

Unscheduled

8 SPONSOR

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9 DATE OF FIRST APPROVAL

23 August 2000

10 DATE OF REVISION

27 September 2021

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SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
6.1	Removal of albumin purity