

Biostate[®]

NAME OF THE MEDICINE

Human coagulation factor VIII and human von Willebrand factor complex, powder for injection.

DESCRIPTION

Biostate[®] is a high purity, sterile, powder for injection containing a human coagulation factor VIII (FVIII) and human von Willebrand factor (VWF) complex. It is prepared from pooled human plasma donated by New Zealand's voluntary non-remunerated donors. It is intended for intravenous administration. The FVIII/VWF complex in Biostate[®] is purified from cryoprecipitate using selective precipitation and size exclusion chromatography steps. The Biostate[®] manufacturing process includes solvent detergent (tributyl phosphate and polysorbate 80) and dry heat treatment (80°C for 72 hours) steps to reduce the potential for viral 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 model viruses for hepatitis B (HBV) and hepatitis C viruses (HCV). The manufacturing process also contributes to inactivation/removal of human parvovirus B19 (B19).

Human albumin is added to Biostate[®] as a stabiliser. Measured prior to the addition of albumin, the specific activity of Biostate[®] is nominally 50 FVIII:C IU/mg of total 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. When expressed as per mg clottable protein (fibrinogen), the specific activity of the final product is nominally 300 IU VWF:RCo/mg and 150 IU FVIII:C/mg, based on the Biostate[®] VWF to FVIII ratio of 2:1.

Biostate[®] is available in two different concentrations (strengths): 50 IU/mL and 100 IU/mL, and in four different presentations as detailed in **Table 1**:

Table 1: Biostate[®] composition

	250 IU (50 IU FVIII/mL)	500 IU (50 IU FVIII/mL)	500 IU (100 IU FVIII/mL)	1000 IU (100 IU FVIII/mL)
Active ingredients IU/vial (nominal)				
FVIII	250	500	500	1000
VWF:RCo	500	1000	1000	2000
Excipients mg/vial				
Albumin stabiliser (≥99% pure)	50	100	50	100
Sucrose	75	150	75	150
Sodium citrate	29	58	29	58
Sodium chloride	17–23	34–46	17–23	34–46
Trometamol	12	24	12	24
Calcium chloride	1.8	3.6	1.8	3.6
Sodium octanoate	1.4	2.8	1.4	2.8
Reconstitution volume (mL)	5	10	5	10

PHARMACOLOGY

The Biostate[®] FVIII/VWF complex consists of two different noncovalently bound proteins: FVIII and VWF. FVIII is an essential cofactor in activation of factor X leading ultimately to the formation of thrombin and fibrin. The activity of FVIII is measured as FVIII:C. VWF promotes platelet aggregation and platelet adhesion on damaged vascular endothelium; it also serves as a stabilising carrier protein for the procoagulant protein FVIII. The activity of VWF is measured as VWF:RCo.

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 as the platelets are prevented from adhering to sub-endothelial tissue. As a result, excessive bleeding may occur.

The VWF:RCo activity in Biostate[®] exists in a 2:1 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 coagulation 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 factor VIII protein. FVIII is a cofactor for activated factor IX, and accelerates 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.

Pharmacokinetics

The pharmacokinetics of Biostate[®] has been studied in adult patients with VWD and haemophilia A, in separate trials.

The pharmacokinetics of FVIII and VWF in Biostate[®] were measured in a single-blind, randomised, multicentre study of 12 patients aged from 19 to 58 years with VWD in whom the response to desmopressin was inadequate, or contraindicated. VWF:Ag, FVIII and HMW multimers were also measured in addition to the pharmacokinetic parameters for the 12 patients in **Table 2**.

Two clinical trials investigated the pharmacokinetics of FVIII in Biostate[®] in patients with haemophilia A. The first trial involved 16 male patients with severe haemophilia A (up to or equal to 2% FVIII) who each received a single dose of 50 IU FVIII/kg body weight. All patients had been previously treated with FVIII concentrates and were aged from 17 to 53 years. The pharmacokinetic data for the 16 patients is summarised in **Table 2** (indicated by the term ‘Initial’).

To assess the potential for development of inhibitors to FVIII which may not be detected by conventional laboratory assays, a repeat pharmacokinetics trial was performed on eight patients who participated in the first pharmacokinetics trial and continued treatment with Biostate[®] for 3–6 months. There was no significant difference in the half-life or recovery determined in this trial compared to the first pharmacokinetics trial (see **Table 2**, indicated by the term ‘Repeat’), thus indicating no inhibitor development with the use of Biostate[®].

Table 2: Pharmacokinetics data (mean values)

Patient Group, No.	Active	Half-life (h)	Recovery (%)	Clearance (mL/h/kg)	Cmax (IU/mL)
VWD (n=12)	VWF:RCo	11.6	85	4.23	1.15
	VWF:CB	12.2	83	4.90	1.03
	FVIII:C	N/A	110	N/A	0.69
Haemophilia A Initial (n=16)	FVIII:C	12.4	108	3.25	1.20
Haemophilia A Repeat (n=8)	FVIII:C	14.1	110	2.98	1.08

N/A: The contribution of endogenous FVIII makes the true pharmacokinetics of the administered FVIII:C impossible to measure.

CLINICAL TRIALS

Von Willebrand Disease

An open-label, multicentre study was undertaken to assess the safety and efficacy of Biostate[®] in the management of surgical procedures, the treatment of non-surgery bleeds and for prophylactic therapy in patients with VWD. Twenty-three patients participated, providing data in 10 major surgeries, 19 minor surgeries, 9 non-surgery bleeds and 4 undergoing prophylaxis.

Haemostatic efficacy was considered excellent or good in the four patients on prophylaxis therapy. Haemostatic efficacy was also considered excellent or good in all the minor and major surgery events and all the non-surgery bleed events with the exception of one patient who experienced a gastrointestinal haemorrhage whose bleeding remained severe and uncontrolled until the third day of treatment. He was transferred to a non-study site hospital to undergo a definitive procedure to stop the bleeding.

In over 80% of the surgical events covered with Biostate[®], blood loss was assessed as less or equivalent to that expected for patients without a bleeding disorder undergoing a similar procedure.

Biostate[®] was effective in increasing plasma levels of FVIII:C, VWF:RCo, VWF:Ag and VWF:CB with normal levels achieved in the majority of the surgery events.

The mean daily doses that achieved haemostatic efficacy were approximately 27, 33, and 41 IU FVIII:C/kg/day for median durations of 2.0, 2.0 and 7.5 days for non-surgery bleed, minor surgery and major surgery events, respectively.

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

Additionally, the clinical efficacy of Biostate[®] in the prevention and control of bleeding in patients with VWD undergoing invasive procedures or surgery was determined in a retrospective review of clinical data obtained from 43 patients (undergoing 58 surgical procedures) who were treated with Biostate[®], at the discretion of their physician. Haemostatic efficacy was assessed as excellent in 78% and good in 22% of procedures in all VWD sub-types. There were no bleeding events attributable to lack of efficacy in any patient.

Haemophilia A

The safety, tolerability and efficacy of Biostate[®] was studied in 30 male patients with severe haemophilia A, including the 16 patients who participated in the first pharmacokinetics trial. All patients had been previously treated with FVIII concentrates, were aged from 16 to 62 years, and were treated with Biostate[®] in this trial on an as required basis for 6 months. The 30 patients received a total of 1,416,550 IU of FVIII (1019 administrations) over the 6 month period, the total dose per person ranging from 6000 IU to 112,250 IU. Out of the 782 administrations which were graded by the patients for efficacy, 124 (16%) were graded as excellent, 491 (63%) as good, 136 (18%) as moderate and 31 (4%) as poor. No patients undergoing surgery were included in this trial. Biostate[®] was well tolerated by all patients. Inhibitor development was monitored during the trial using the Bethesda assay. Inhibitors were not detected in any of the 30 patients.

Adverse reactions encountered during the clinical trials in haemophilia A patients are outlined under **ADVERSE EFFECTS**.

Biostate[®] has not been studied in previously untreated patients.

INDICATIONS

Biostate[®] is indicated for:

- the treatment and prophylaxis of haemorrhage or surgical bleeding in VWD when desmopressin (DDAVP) treatment alone is ineffective or contraindicated
- the treatment and prophylaxis of bleeding associated with FVIII deficiency due to haemophilia A.

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.

PRECAUTIONS

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. 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 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.

Effects on fertility

Animal reproduction studies have not been conducted with Biostate[®].

Paediatric use

The use of Biostate[®] in the paediatric population has not been established in clinical studies.

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

Use in the elderly

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

Carcinogenicity and genotoxicity

No carcinogenicity or genotoxicity studies have been conducted with Biostate[®].

Effect on laboratory tests

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

INTERACTIONS WITH OTHER MEDICINES

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

ADVERSE EFFECTS

The following tabulated adverse reactions 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 $\geq 1/10$

Common $\geq 1/100$ and $<1/10$

Uncommon $\geq 1/1000$ and $<1/100$

Rare $\geq 1/10,000$ and $<1/1000$

Very rare $< 1/10,000$

Not known frequency cannot be estimated from the available data.

Table 3: 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 **PRECAUTIONS**.

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 of suspected adverse reactions

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

DOSAGE AND ADMINISTRATION

Dosage

The dosage recommendations in **Table 4** (VWD) and **Table 5** (haemophilia A) 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.

Table 4: VWD dosage guidelines*

Indication	Dose (IU/kg)		Dose frequency	Target FVIII/VWF (%) (IU/dL)
	FVIII:C	VWF:RCo		
Spontaneous bleeding episodes	12.5–25	25–50	initial	VWF peak level >50%, FVIII >30%
	12.5	25	subsequent every 12–24 hours	VWF/FVIII trough levels of >30% until bleeding stops (usually, 2–4 days)
Minor surgery	30	60	daily	VWF/FVIII trough levels of >30% until healing is complete (usually, 2–4 days)
Major surgery	30–40	60–80	initial	VWF peak level >100%, FVIII >60%
	15–30	30–60	subsequent every 12–24 hours	VWF/FVIII trough levels of >50% until healing is complete (usually, 5–10 days)
Prophylaxis	12.5–20	25–40	3 times weekly	trough 1

* For patients with severely reduced VWF levels e.g. <10% of normal (doses may need to be adjusted down if baseline levels are >20%).

Table 5: Haemophilia A dosage guidelines

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

Continuous infusion

No studies using continuous infusion were 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 concentrations be determined in patient's plasma at suitable intervals and during the treatment of severe haemorrhage.

Reconstitution

1. Before reconstitution allow the vials of Biostate[®] and Water for Injections to reach a temperature between 20°C and 30°C.
2. Remove the caps from the tops of the Biostate[®] and Water for Injections vials.
3. Apply a suitable antiseptic to the exposed part of the rubber stoppers of both Biostate[®] and Water for Injections and allow to dry.
4. Open the outer package of the Mix2Vial[™] filter transfer set by peeling away the lid. **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 the New Zealand Blood Service.** Place the Water for Injections on a level surface and hold the vial firmly. Take the Mix2Vial[™] together with its outer package and invert it. Push the blue plastic cannula of the Mix2Vial[™] firmly through the rubber stopper of the Water for Injections. See **Figure 1**.
5. While holding onto the vial of Water for Injections, carefully remove the outer package from the Mix2Vial[™], being careful to leave the Mix2Vial[™] attached firmly to the Water for Injections vial. Ensure that only the package and not the Mix2Vial[™] is removed. See **Figure 2**.

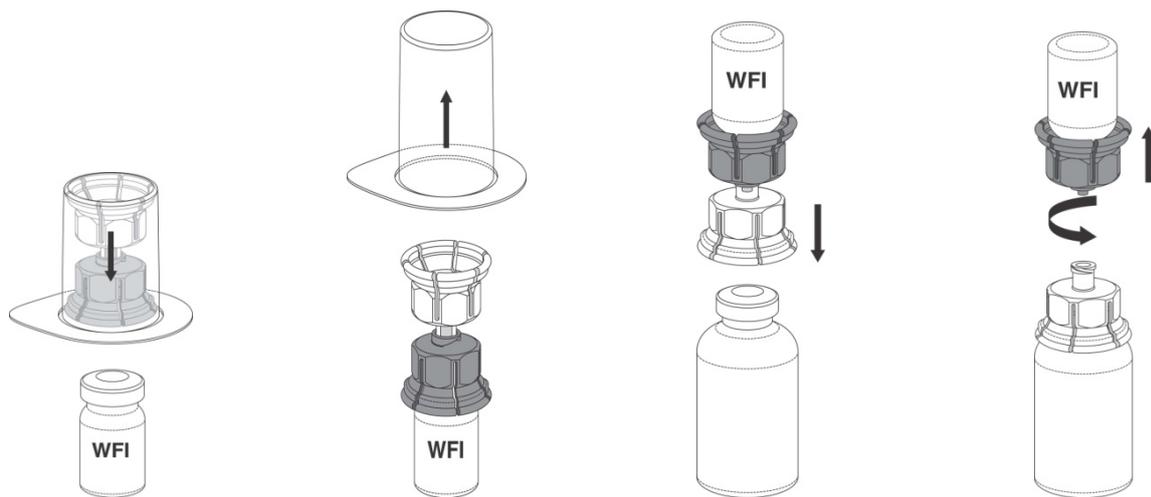


Figure 1

Figure 2

Figure 3

Figure 4

Note: WFI = Water for Injections

6. With the Biostate[®] vial held firmly on a level surface, invert the Water for Injections with the Mix2Vial[™] attached and push the transparent plastic cannula end of the Mix2Vial[™] firmly through the Biostate[®] stopper. See **Figure 3**. The water will be drawn into the vial by the vacuum within. **In the unlikely event that the vial does not contain a vacuum, do not use the product, but return it to the New Zealand Blood Service.**
7. With the Water for Injections and Biostate[®] vials still attached, gently swirl the product vial to ensure the product is fully dissolved. Avoid excessive frothing. A clear or slightly opalescent solution is usually obtained within 2 to 5 minutes. The solution should be used as described in **Administration**.
8. Once the contents of the Biostate[®] vial are completely dissolved, firmly hold both the transparent and blue parts of the Mix2Vial[™]. Unscrew the Mix2Vial[™] into two separate pieces (see **Figure 4**), and discard the empty Water for Injections vial and the blue part of the Mix2Vial[™] in an appropriate waste container.

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.

CAUTION

The product does not contain an antimicrobial preservative. It must, therefore, be used within three hours after reconstitution. Any unused solution should be discarded appropriately. Use in one patient on one occasion only. If a clot or gel forms, do not use the product but return it to the New Zealand Blood Service.

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 (usually within 5 minutes, or as tolerated by the patient) by the intravenous route. When the contents of more than one vial are to be given, it will be convenient to pool the total amount prior to administration in a large syringe or sterile bag. This must be done aseptically.
4. To reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. The solution must not be stored and, unless reconstitution has been done under aseptic conditions and sterile integrity of the delivery device has been maintained, infusion should be completed within three hours of reconstitution in the case of routine use. 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.
5. 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[®].

Spillage or 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.

OVERDOSAGE

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.

PRESENTATION AND STORAGE CONDITIONS

Biostate[®] powder for injection is packaged as:

- 250 IU vial of Biostate[®] (50 IU FVIII per mL), 5 mL vial of Water for Injections, and one Mix2Vial[™] filter transfer set
- 500 IU vial of Biostate[®] (50 IU FVIII per mL), 10 mL vial of Water for Injections, and one Mix2Vial[™] filter transfer set
- 500 IU vial of Biostate[®] (100 IU FVIII per mL), 5 mL vial of Water for Injections, and one Mix2Vial[™] filter transfer set
- 1000 IU vial of Biostate[®] (100 IU FVIII per mL), 10 mL vial of Water for Injections and one Mix2Vial[™] filter transfer set.

Not all presentations may be supplied.

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.

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE

General Sale Medicine

DATE OF PREPARATION

17 March 2016

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