

Biostate[®]

Singapore

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. Biostate[®] is manufactured from plasma donated by Singapore's voluntary and 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 presentations as detailed in **Table 1**:

Table 1: Biostate[®] composition

| | 250 IU FVIII / 500 IU VWF | 500 IU FVIII / 1000 IU VWF |
|---|--------------------------------------|---------------------------------------|
| Active ingredients IU/vial (nominal) | | |
| FVIII | 250 | 500 |
| VWF:RCo | 500 | 1000 |
| Excipients mg/vial | | |
| Albumin stabiliser (≥99% pure) | 50 | 100 |
| Sucrose | 75 | 150 |
| Sodium citrate | 29 | 58 |
| Sodium chloride | 17–23 | 34–46 |
| Trometamol | 12 | 24 |
| Calcium chloride | 1.8 | 3.6 |
| Sodium octanoate | 1.4 | 2.8 |
| Reconstitution volume (mL) | 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 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. 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 pharmacokinetics 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. | | Half-life (h) | Recovery (%) | Clearance (mL/h/kg) | Cmax (IU/mL) |
|------------------------------|---------------------|---------------|--------------|---------------------|--------------|
| VWD (n=12) | VWF:RC ₀ | 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

The efficacy of Biostate[®] in the control of surgical bleeding was assessed in an open-label non-controlled trial in 23 patients (7 VWD Type 3). A 4-point rating scale was used: 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 9 patients undergoing 10 major surgical procedures, the efficacy was excellent in 7 (70%) and good in 3 (30%). In 11 patients undergoing 15 minor surgical procedures, haemostatic efficacy was excellent in 14 (93%) and good in 1 (7%). The mean Biostate[®] dose to achieve haemostasis was 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 a retrospective review of Biostate[®] in surgical bleeding in 43 patients undergoing 58 procedures, the haemostatic efficacy was excellent in 78% of procedures and good in 22%. Efficacy in the VWD Type 3 patients (n=5) was rated as excellent in 55%. The mean Biostate[®] 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.

The efficacy and safety of Biostate[®] has not been established in acquired VWD.

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

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 789 administrations which were graded by the patients for efficacy, 131 (17%) were graded as excellent, 490 (62%) as good, 137 (17%) 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 prevention of bleeding in surgical or invasive procedures in patients with von Willebrand disease when desmopressin (DDAVP) treatment 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 its components.

PRECAUTIONS

Biostate[®] should be used with caution in patients with a known allergy to FVIII and/or VWF concentrates, or human albumin. Allergic, anaphylactic reactions or fever are rarely observed in patients receiving FVIII preparations. If any adverse event occurs while Biostate[®] is being administered, the rate of injection should be slowed or stopped to alleviate symptoms.

Patients should be informed of the early signs of hypersensitivity reactions such as allergic skin reactions including hives, generalised urticaria, tightness of the chest, wheezing, flushing, hypotension and anaphylaxis. If these symptoms occur they should be advised to seek medical opinion. In case of shock, the current medical standards for treatment of shock should be instituted.

The formation of neutralising antibodies (inhibitors) to FVIII is a known complication in the management of individuals with haemophilia A. These inhibitors are immunoglobulins (usually IgG) directed against the FVIII procoagulant activity. The inhibitor level in the plasma is measured by the Bethesda assay (as Bethesda Units (BU) per mL). The risk of developing inhibitors is correlated to the exposure to 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.

Patients with VWD, especially type 3 patients, may very rarely develop inhibitors to VWF. If such inhibitors occur, the condition would manifest itself as an inadequate clinical response such as bleeding not being controlled with an appropriate dose or the expected VWF:RCO activity plasma levels not being attained. Such antibodies may occur in close association with anaphylactic reactions. Therefore, patients experiencing anaphylactic reaction should be evaluated for the presence of an inhibitor.

Thromboembolic events have been rarely reported in VWD patients receiving coagulation factor replacement therapy, especially in the setting of known risk factors for thrombosis and may be related to the generation of supranormal FVIII levels. In these patients, caution should be exercised and antithrombotic measures 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. 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 current procedures applied in the manufacture of this product are effective against enveloped viruses such as HIV, HBV and HCV viruses, and the non-enveloped virus HAV. They are also known to contribute to the inactivation/removal of the non-enveloped virus, B19.

Despite these safety 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 hepatitis A and hepatitis B should be considered where appropriate, for patients in receipt of medicinal products from human plasma.

Effects on fertility

The effects of Biostate[®] on fertility are unknown.

Use in pregnancy

The use of Biostate[®] during pregnancy has not been established in clinical trials.

Use in lactation

The effects of Biostate[®] on lactation are unknown.

Paediatric use

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

Use in the elderly

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

Carcinogenicity

The effects of Biostate[®] on carcinogenicity are unknown.

Genotoxicity

The effects of Biostate[®] on genotoxicity are unknown.

Interactions with other medicines

The interaction of Biostate[®] with other drugs has not been established in specific studies.

Effect on laboratory tests

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

ADVERSE EFFECTS

Allergic reactions or fever are rarely observed in patients receiving FVIII/VWF preparations. If any adverse event occurs while Biostate[®] is being administered, the rate of injection should be slowed or stopped to alleviate symptoms.

Adverse events in clinical trials

Von Willebrand Disease

In the Biostate[®] pharmacokinetics clinical study, adverse events were reported by 11 out of the 12 VWD patients. Most events were mild to moderate in severity and considered not related to Biostate[®]. Nine adverse events were considered by the investigator to be related to Biostate[®] and were reported by two of the 12 patients (refer to **Table 3** for a summary of the related adverse events).

In the safety and efficacy trial, 22 of the 23 VWD patients experienced adverse events. Only three events were considered by the investigator to be probably or possibly related to Biostate[®] (refer to **Table 3** for summary of related adverse events). Two serious adverse events were reported: iliacus myositis and upper respiratory tract infection, both considered unrelated to Biostate[®]. All other adverse events were considered unrelated or unlikely to be related to Biostate[®].

Haemophilia A

In the initial pharmacokinetics clinical trial, only one of the 16 haemophilia A patients experienced two adverse events. Both events were single episodes, mild in severity and considered to be related to Biostate[®] (refer to **Table 3** for a summary of the related adverse events).

In the tolerability, safety and efficacy clinical trial, 21 of the 30 haemophilia A patients experienced adverse events. Twenty-three of the adverse events were considered to be related or possibly related to Biostate[®] (refer to **Table 3** for a summary of the related adverse events). One of the patients who experienced back pain and skeletal pain during the safety and efficacy trial also experienced these symptoms during the initial pharmacokinetics trial. All of these related adverse events were considered to be mild in severity.

Table 3: Clinical trial related adverse events

| MedDRA Standard System Organ Class | VWD | Haemophilia A |
|--|-------------------------------|--|
| Gastrointestinal disorders | Vomiting, nausea | - |
| General disorders and administration site conditions | Pyrexia | Fever, headache |
| Investigations | Liver function test abnormal | - |
| Musculoskeletal and connective tissue disorders | - | Back pain, chest pain, arthralgia, skeletal pain |
| Nervous system disorders | Dizziness, dysgeusia, syncope | Anxiety, dizziness |
| Skin and subcutaneous tissue disorders | Sweating | - |
| Respiratory, thoracic and mediastinal disorders | Dyspnoea | - |
| Vascular disorders | Thrombophlebitis | Flushing |

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:RC _o | | |
| 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) |

* 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 20–25 | single dose 8–12 hourly | 1 2–10 | peak >100 trough 80–100 |
| 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 top 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 appropriate Blood Transfusion 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 mL Water for Injections is provided for 250 IU vial, 10 mL Water for Injections is provided for 500 IU vial).

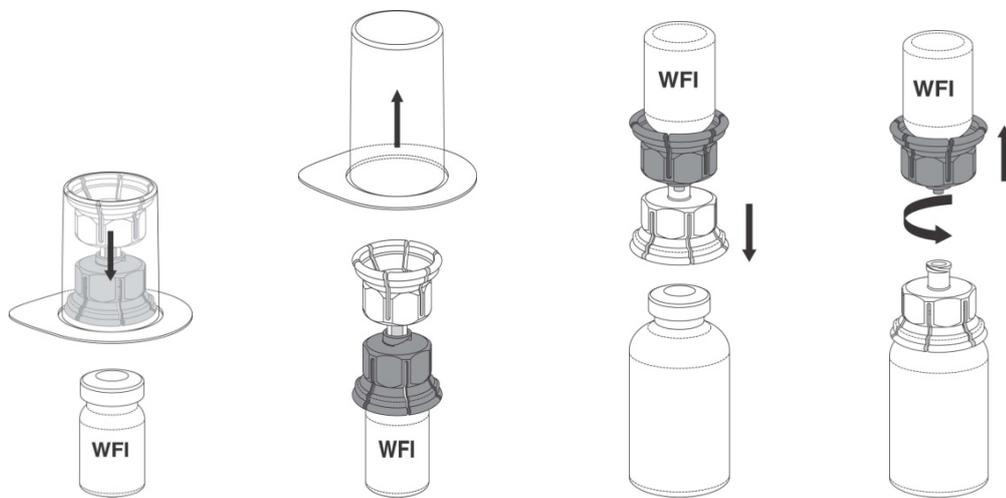


Figure 1

Figure 2

Figure 3

Figure 4

WFI = Water for Injections

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**.
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 appropriate Blood Transfusion 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 appropriate Blood Transfusion 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

No symptoms of overdose with human plasma coagulation FVIII/VWF concentrates are known.

PRESENTATION AND STORAGE CONDITIONS

Biostate[®] powder for injection is packaged as:

- 250 IU FVIII/500 IU VWF vial of Biostate[®], 5 mL vial of Water for Injections, and one Mix2Vial[™] filter transfer set
- 500 IU FVIII/1000 IU VWF vial of Biostate[®], 10 mL vial of Water for Injections, and one Mix2Vial[™] filter transfer set.

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

NAME AND ADDRESS OF THE MANUFACTURER

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For

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