

AUSTRALIAN PRODUCT INFORMATION

OBIZUR® (susoctocog alfa)

1 NAME OF THE MEDICINE

Susoctocog alfa (bhk).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each OBIZUR vial contains nominally 500 units (U) of susoctocog alfa, which is a B domain deleted recombinant derived antihæmophilic factor VIII (rpFVIII), porcine sequence.

After reconstitution, OBIZUR contains nominally 500 U/mL susoctocog alfa.

Each vial of OBIZUR is labelled with the actual rpFVIII activity expressed in units determined by a one-stage clotting assay, using a reference rpFVIII material calibrated against the World Health Organization (WHO) 8th International Standard for human factor VIII concentrates. The specific activity of OBIZUR is in the range of 11000 - 18000 Units per milligram of protein. The potency values of OBIZUR determined by the chromogenic assay vary and are approximately 20-50 % lower than those of the one-stage clotting assay.

Susoctocog alfa is expressed in a genetically engineered baby hamster kidney (BHK) cell line and secreted into the cell culture medium, and the protein is purified using a series of chromatography and filtration steps. The production process includes two dedicated viral clearance steps - a solvent/detergent treatment step for viral inactivation and a nanofiltration step through a series of two 15-nm filters for removal of viruses. No additives of human or animal origin are used in the formulation of OBIZUR.

Excipient(s) with known effect

Each vial of OBIZUR contains maximally 4.4 mg (198 mM) sodium per mL of reconstituted solution (see Section 4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE).

For the full list of excipients, see Section 6.1 LIST OF EXCIPIENTS.

3 PHARMACEUTICAL FORM

Powder and diluent for solution for injection

OBIZUR is formulated as a white, sterile, non-pyrogenic, lyophilised powder for intravenous injection after reconstitution with the diluent.

The diluent, water for injections, is a clear and colourless solution, practically free from visible particles.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

OBIZUR, antihaemophilic factor (recombinant), porcine sequence, is a recombinant DNA derived, antihaemophilic factor indicated for the treatment of bleeding episodes in adults with acquired haemophilia A.

Safety and efficacy of OBIZUR have not been established in patients with baseline anti-porcine factor VIII inhibitor titre greater than 20 Bethesda Units (BU).

OBIZUR is not indicated for the treatment of congenital haemophilia A or von Willebrand disease.

4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment with OBIZUR under the supervision of a physician experienced in the treatment of bleeding disorders is recommended.

For prescribed doses of OBIZUR, “units” should be written in full.

The product is for single use in one patient only. Discard any residue.

Dosage, frequency, and duration of treatment with OBIZUR depends on the severity of bleeding episode, target factor VIII levels, and the patient’s clinical condition.

Parenteral drug products should be inspected for particulate matter and discolouration prior to administration. Do not administer if particulate matter or discoloration is found; contact Takeda Customer Service.

Dose

- Dose, dosing frequency, and duration of treatment with OBIZUR depend on the location and severity of bleeding episode, target factor VIII levels, and the patient’s clinical condition. Monitor replacement therapy in cases of major surgery or life-threatening bleeding episodes.
- Each vial of OBIZUR has the recombinant porcine factor VIII potency in units stated on the vial.
- Patients may vary in their pharmacokinetic (e.g. half-life, *in vivo* recovery) and clinical responses. Titrate dose and frequency based on factor VIII recovery levels and individual clinical response.

A guide for dosing OBIZUR for the treatment of bleeding episodes is provided in Table 1. Maintain the factor VIII activity within the target range. Plasma levels of factor VIII should not exceed 200% of normal or 200 units per dL.

Table 1: Dosing for Treatment of Bleeding Episodes

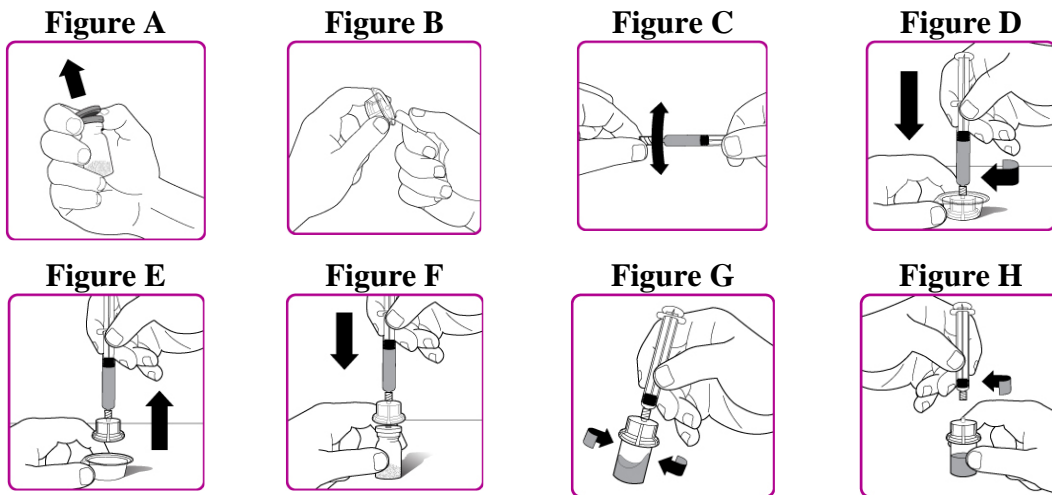
Type of Bleeding	Factor VIII Level Required (Units per dL or % of normal)	Initial Dose (Units per kg)	Subsequent Dose	Frequency and Duration of Subsequent Dosing
Minor and Moderate Superficial muscle / no neurovascular compromise, and joint	50-100	200	Titrate subsequent doses to maintain recommended factor VIII trough levels and individual clinical response	Dose every 4 to 12 hours, frequency may be adjusted based on clinical response and measured factor VIII levels
Major Moderate to severe intramuscular bleeding, retroperitoneal, gastrointestinal, intracranial	100-200 (To treat an acute bleed) 50-100 (After acute bleed is controlled, if required)			

Reconstitution

Use aseptic technique during the reconstitution procedure.

If the patient needs more than one vial of OBIZUR per injection, reconstitute each vial according to the following instructions:

1. Bring the OBIZUR vial and the prefilled diluent syringe to room temperature.
2. Remove the plastic cap from the OBIZUR vial (Figure A).
3. Wipe the rubber stopper with an alcohol swab (not supplied) and allow it to dry prior to use.
4. Peel back the cover of the vial adapter package (Figure B). Do not touch the luer-lock (tip) in the center of the vial adapter. Do not remove the vial adapter from the plastic package.
5. Place the vial adapter package on a clean surface with the luer-lock pointing up.
6. Snap off the tamper resistant cap of the prefilled syringe (Figure C).
7. While firmly holding the vial adapter package, connect the prefilled syringe to the vial adapter by pushing the syringe tip down onto the luer lock in the center of the vial adapter, and turning it clockwise until the syringe is secured. Do not over tighten (Figure D).
8. Remove the plastic package (Figure E).
9. Place the OBIZUR vial on a clean, flat, hard surface. Place the vial adapter over the OBIZUR vial and firmly push the filter spike of the vial adapter through the center of the rubber circle until the clear plastic cap snaps onto the vial (Figure F).
10. Push the plunger down to slowly inject all of the diluent from the syringe into the OBIZUR vial.
11. Gently swirl (in a circular motion) the OBIZUR vial without removing the syringe until all of the powder is fully dissolved (Figure G). The reconstituted solution should be inspected visually for particulate matter before administration. Do not use if particulate matter or discoloration is observed.
12. With one hand hold the vial and vial adapter, and with the other hand firmly grasp the barrel of the prefilled syringe and in a counter-clockwise motion unscrew the syringe from the vial adapter (Figure H).
13. Use OBIZUR within 3 hours after reconstitution when stored at room temperature.



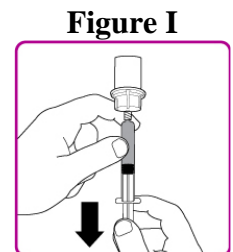
Administration

For intravenous injection only.

Inspect the reconstituted OBIZUR solution for particulate matter and discoloration prior to administration. The solution should be clear and colourless in appearance. Do not administer if particulate matter or discoloration is observed.

Do not administer OBIZUR in the same tubing or container with other medicinal products for infusion.

1. Once all vials have been reconstituted, connect a large syringe to the vial adapter by gently pushing the syringe tip down onto the luer lock in the center of the vial adapter, and turning clockwise until the syringe is secured.
2. Invert the vial; push the air in the syringe into the vial and withdraw the reconstituted OBIZUR into the syringe (Figure I).
3. Unscrew the large syringe counter-clockwise from the vial adapter, and repeat this process for all reconstituted vials of OBIZUR until the total volume to be administered is reached.
4. Administer the reconstituted OBIZUR intravenously at a rate of 1 to 2 mL per minute.



4.3 CONTRAINDICATIONS

OBIZUR is contraindicated in patients who have had life-threatening hypersensitivity reactions to OBIZUR or its components (including traces of hamster proteins).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Hypersensitivity reactions

Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the injection site, chills, flushing, generalised urticarial, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) are possible and may progress to severe anaphylaxis (including shock).

Immediately discontinue administration and initiate appropriate treatment if allergic or anaphylactic-type reactions occur.

Inhibitory antibodies

Inhibitory antibodies to OBIZUR have occurred in patients treated with OBIZUR. Monitor patients for the development of antibodies to OBIZUR by appropriate assays (see Section 4.8 ADVERSE EFFECTS). If the plasma factor VIII level fails to increase as expected, or if bleeding is not controlled after OBIZUR administration, suspect the presence of an anti-porcine factor VIII antibody. Anamnestic reactions with rise in human factor FVIII and/or recombinant factor VIII, porcine sequence inhibitors have also been reported in patients treated with OBIZUR. These anamnestic rises may result in lack of response to OBIZUR. If such inhibitory antibodies to porcine factor VIII are suspected and there is a lack of clinical response, consider other therapeutic options.

Monitoring laboratory tests

Perform one-stage clotting assay to confirm that adequate factor VIII levels have been achieved and maintained (see Section 4.2 DOSE AND METHOD OF ADMINISTRATION).

- Monitor factor VIII activity 30 minutes and 3 hours after initial dose.
- Monitor factor VIII activity 30 minutes after subsequent doses.

Monitor the development of inhibitory antibodies to OBIZUR. Perform a Nijmegen Bethesda inhibitor assay if expected plasma factor VIII activity levels are not attained or if bleeding is not controlled with the expected dose of OBIZUR. Use Bethesda Units (BU) to report inhibitor levels.

Others

High and sustained factor VIII activity in blood may predispose to thromboembolic events. Those with pre-existing cardiovascular disease and the elderly are at particular risk.

OBIZUR contains maximally 4.4 mg (198 mM) sodium per 500 unit (nominal) vial. This should be taken into consideration by patients on a controlled sodium diet.

Use in the elderly

Of the 29 subjects within the trial, the average age was 70 years of age. Nineteen subjects were 65 years of age or older. Clinical studies suggest that OBIZUR is safe and effective in the adult population (see Section 4.8 ADVERSE EFFECTS and Section 5.1 PHARMACODYNAMIC PROPERTIES, Clinical trials). While no differences were observed between geriatric and adult responses to OBIZUR, these findings are inconclusive given the small number of subjects enrolled in either group.

Dose adjustments in the geriatric population have not been studied. Specific hazards associated with the concomitant use of OBIZUR with other drugs in the elderly population have not been studied in the clinical trial.

Paediatric use

The safety and efficacy of OBIZUR have not been established in paediatric patients.

Use in children [from 0 (birth) to <18 years] with congenital or in rare cases acquired haemophilia is currently not approved.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No interactions of OBIZUR with other medicinal products are known.

No interaction studies have been performed with OBIZUR. Further, no interactions of OBIZUR with other medicinal products have been reported.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The effects of OBIZUR on fertility have not been established.

Use in pregnancy

Australian Pregnancy Categorisation (Category B2)

There are no adequate or well-controlled studies with OBIZUR, or other recombinant factor VIII products, in pregnant women. Studies in pregnant animals have not been conducted with susoctocog alfa. Therefore, OBIZUR should only be used in pregnant women if clearly needed.

Use in lactation

It is not known whether OBIZUR is excreted into human milk. Because many drugs are excreted into human milk, caution should be exercised if OBIZUR is administered to breastfeeding mothers.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

There is no information of the effects of OBIZUR on the ability to drive or use machines.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Adverse reactions from clinical trials

In the clinical trial of OBIZUR for acquired haemophilia A, 29 adult subjects were evaluable for safety. Of the 29 adult subjects, ten were between the ages of 42 and 65, and 19 were 65 years of age or older. Ten (34%) subjects were female.

In the clinical trial, no serious adverse reactions (AR) occurred. Non-serious ARs occurred in 2 subjects (6.9%). These two subjects developed anti-porcine factor VIII inhibitors (≥ 0.6 BU) that were considered an AR to OBIZUR by the investigator because treatment was discontinued after 24 hours of detection of the inhibitor.

Table 2: Clinical Trial Adverse Reactions

System Organ Class (SOC)	Preferred MedDRA Term (Version 18.0)	# of ARs	Number of Subjects (N=29)	Frequency	% per Subject
INVESTIGATIONS	Antibody test positive	2	2	Common	6.9%

Legend: ADR frequency is based upon the following scale: Very Common ($\geq 1/10$); Common ($\geq 1/100 - < 1/10$), Uncommon ($\geq 1/1,000 - < 1/100$), Rare ($\geq 1/10,000 - < 1/1,000$), Very Rare ($< 1/10,000$)

Immunogenicity

All subjects were monitored for development of inhibitory antibodies to OBIZUR using the Nijmegen modification of the Bethesda inhibitor assay. A subject was considered to have developed an OBIZUR inhibitor if the titre was ≥ 0.6 BU/mL.

Of the 29 subjects treated with OBIZUR, 19 subjects were negative for anti-porcine factor VIII antibodies at baseline. Five of the 19 (26%) developed anti-porcine factor VIII antibodies following exposure to OBIZUR. Of the 10 subjects with detectable anti-porcine factor VIII antibodies at baseline, 2 (20%) experienced an increase in titre and eight (80%) experienced a decreasing to a non-detectable titre.

All subjects were also monitored for development of binding antibodies to baby hamster kidney (BHK) protein by a validated sequential ELISA (enzyme-linked immunosorbent assay). No patients developed de novo anti-BHK antibodies.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralising antibody) positivity in an assay may be influenced by several factors, including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to OBIZUR with the incidence of antibodies to other products may be misleading.

Post-marketing adverse reactions

The table below presents the System Organ Class (SOC) and Adverse Drug Reactions (ADR) that have been reported from post-marketing experience.

Table 3: ADRs from Post-Marketing Experience for which the Frequency is Unknown

System Organ Class (SOC)	Preferred Term (PT) MedDRA version 22.0
IMMUNE SYSTEM DISORDERS	Anamnestic Reaction

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

No symptoms of overdose have been reported.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: antihæmorrhagics, blood coagulation factor VIII, porcine sequence

ATC code: B02BD14

Mechanism of action

Patients with acquired hæmophilia A have normal factor VIII genes but develop auto-antibodies against their own factor VIII (i.e. inhibitors). These auto-antibodies neutralise circulating human factor VIII and create a functional deficiency of this pro-coagulant protein. Acquired hæmophilia A results in a prolonged clotting time as measured by the activated partial thromboplastin time (aPTT) assay, a conventional in vitro test for biological activity of factor VIII.

Treatment with OBIZUR should normalise the aPTT during treatment; however aPTT normalisation should not be used as a measure of efficacy. Once susoctocog alfa is activated, the resulting molecule has a comparable activity to the endogenous human activated factor VIII.

Clinical trials

The efficacy of OBIZUR for the treatment of serious bleeding episodes in subjects with acquired hæmophilia A was investigated in a prospective, open-label trial (N=29). The trial was conducted in 18 Caucasian, 6 African-American, and 5 Asian subjects diagnosed with acquired hæmophilia A, having auto-immune inhibitory antibodies to human factor VIII, and experiencing serious bleeding episodes that required hospitalisation. Subjects with a prior history of bleeding disorders other than acquired hæmophilia A, anti-porcine factor VIII antibody titre > 20 BU, or in whom the bleeding episode was judged likely to resolve on its own were excluded. One subject was considered evaluable at study entry; however, it was later determined that this subject did not have acquired hæmophilia A, leaving 28 subjects evaluable for efficacy.

An initial dose of 200 units per kg OBIZUR was administered to subjects for the treatment of life- or limb-threatening initial bleeding episodes. Patients were treated with OBIZUR until resolution of bleeding or dosing was continued at the physician's discretion according to the clinical assessment. These bleeding episodes included 19 intramuscular or joint bleeding episodes, 4 post-surgical bleeding episodes, 2 intracranial episodes, 2 surgeries, 1 retroperitoneal hæmorrhage, and 1 periorbital bleed. Haemostatic response was assessed by the study site investigator at specified time points after initiation of OBIZUR treatment using a pre-specified rating scale that was based on subjective clinical assessments combined with objective factor VIII activity levels achieved. An assessment of effective or partially effective was considered as a positive response (see Table 4 for definitions).

Table 4: Response to OBIZUR Treatment Evaluation

Assessment of efficacy	Control of bleeding	Clinical Assessment	Factor VIII levels	Response
Effective	bleeding stopped	clinical control	≥50%	positive
Partially effective	bleeding reduced	clinical stabilisation or improvement; or alternative reason for bleeding	≥ 20%	positive
Poorly effective	bleeding slightly reduced or unchanged	not clinically stable	<50%	negative
Not effective	bleeding worsening	clinically deteriorating	<20%	negative

Of the 28 subjects evaluable for efficacy, all subjects had a positive response to treatment for the initial bleeding episodes at 24 hours after dosing. A positive response was observed in 95% (19/20) of subjects evaluated at 8 hours and 100% (18/18) at 16 hours.

In addition to response to treatment, the overall treatment success was determined by the investigator based on his/her ability to discontinue or reduce the dose and/or dosing frequency of OBIZUR. A total of 24/28 (86%) had successful treatment of the initial bleeding episode. Of those subjects treated with OBIZUR as first-line therapy, defined as no immediate previous use of antihaemorrhagic agents prior to the first OBIZUR treatment, 16/17 (94%) had eventual treatment success reported. Eleven subjects were reported to have received antihaemorrhagics (e.g. rFVIIa, activated prothrombin-complex concentrate, tranexamic acid) prior to first treatment with OBIZUR. Of these 11 subjects, eight had eventual successful treatment (73%).

The median dose per infusion to successfully treat the primary bleeding episode was 133 units per kg and a median total dose of 1523 units per kg. In the initial 24 hour period, a median of 3 infusions (median dose 200 U/kg) were utilised in the clinical study. When treatment was required beyond 24 hours, a median of 10.5 infusions (median dose 100 U/kg) were given for a median of 6 days to control a bleeding episode.

5.2 PHARMACOKINETIC PROPERTIES

Pharmacokinetic (PK) data on OBIZUR are limited and were obtained from 5 subjects in a safety and efficacy study of OBIZUR for the treatment of serious bleeding episodes in subjects with acquired haemophilia with autoimmune inhibitory antibodies to human factor VIII was investigated in a prospective, open-label trial (N=29). The trial was conducted in 18 Caucasian, African-American, and 5 Asian subject(s) experiencing serious bleeding requiring hospitalisation.

All blood draws were done while the subject was in a non-bleeding state. For each subject $t_{1/2}$, T_{max} , A_{max} , AUC from time 0 to last measurement (AUC_{0-t}), AUC_{0-inf} , CL, and the volume of distribution at steady state are presented. Mean values for each parameter are also presented.

For the final dose PK analysis, the % relative factor VIII activity data from the one-stage assays are presented as baseline-corrected values. The individual and summary PK parameters are presented in Table 5.

**Table 5: Individual and Summarised PK Parameter Values for
Factor VIII Baseline-Corrected Concentration Data
after Administration of the final (PK) dose of OBIZUR for the One-Stage Assay Data**

Subject	Dose (U)	t _{1/2} (h)	T _{max} (h)	A _{max} (%)	AUC _{0-t} (%·t)	AUC _{0-∞} (%·t)	CL (U/%·t)	V _{ss} (U/%)
1	5000	3.8	0.42	124	1005	1042	4.80	30.7
2	2934	4.3	0.42	82	299	479	6.13	37.1
2 ^a	2934	4.1	0.42	74	293	460	6.38	37.3
3	7540	3.6	0.45	71	393	404	18.64	95.2
4	9720	1.8	0.50	53	122	135	56.06	135.3
5 ^b	10000	4.2	0.75	178	1583	1686	2.97	21.0
	N	5	5	5	5	5	5	5
	Mean	3.5	0.44	81	423	500	18.07	65.1
	SD	1.0	0.04	26	340	325	21.78	45.1

^a These parameters were generated using the data from the repeated assay.

^b These data are not included in the summary statistics.

A_{max} = maximum observed % activity; AUC_{0-t} = area under the concentration-time curve from time 0 to the last measurable concentration; AUC_{0-∞} = area under the concentration-time curve from time 0 extrapolated to infinity; CL = clearance; t_{1/2} = terminal half-life; T_{max} = time of maximum observed % activity; and V_{ss} = volume of distribution at steady state.

The summary parameters indicate a maximal activity of OBIZUR (T_{max}) at about 26 minutes, with a mean terminal half time (t_{1/2}) of 3.5 hours after dosing. The data are consistent with OBIZUR following first order elimination.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Genotoxicity studies have not been conducted which is acceptable for a biotechnology-derived product such as OBIZUR.

Carcinogenicity

Carcinogenicity studies have not been conducted which is acceptable for a biotechnology-derived product such as OBIZUR.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Polysorbate 80
Sodium chloride
Calcium chloride dihydrate
Sucrose
Trometamol
Sodium citrate dihydrate
Water for injections (diluent)

6.2 INCOMPATIBILITIES

Incompatibility studies have not been performed with OBIZUR. In the absence of compatibility studies with OBIZUR, this medicinal product should not be mixed with other medicinal products.

6.3 SHELF LIFE

3 years.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store in a refrigerator (2°C – 8°C). Do not freeze.

Do not use beyond the expiration date.

Storage after reconstitution

The reconstituted product should be used immediately, but no longer than 3 hours after reconstitution.

6.5 NATURE AND CONTENTS OF CONTAINER

Each pack of OBIZUR contains 1, 5 or 10 each of the following:

- powder vial(s) of 500 units susoctocog alfa
- diluent prefilled syringe(s) of 1 mL water for injections
- vial adapter(s) with filter.

Both the powder vial and the diluent prefilled syringe are supplied in type 1 glass with butyl rubber stopper.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Susoctocog alfa is a purified glycoprotein with an approximate molecular weight of 170 kDa, containing a 90 kDa heavy chain and a 80 kDa light chain. The B-domain normally present in naturally occurring porcine factor VIII has been replaced with a twenty-four amino acid linker.

CAS number

1339940-90-7.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Unscheduled (Exempted)

8 SPONSOR

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9 DATE OF FIRST APPROVAL

29 April 2016 (AUST R 236475)

10 DATE OF REVISION

16 November 2020

Summary table of changes

Section Changed	Summary of new information
4.2, 8	Change of Sponsor

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