OBIZUR
Susoctocog alfa

NAME OF THE MEDICINE

Recombinant porcine coagulation factor VIII, B-domain deleted, Susoctocog alfa (bhk).


DESCRIPTION

The active ingredient in OBIZUR is a recombinant (r) analogue of porcine factor VIII (pFVIII) with an approximate molecular weight of 170 kDa. The rpFVIII molecule in OBIZUR is a glycoprotein 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. Once activated, the resulting rpFVIIIa has a comparable activity to the endogenous human FVIIIa.

OBIZUR is expressed in a genetically engineered baby hamster kidney (BHK) cell line which secretes rpFVIII into the cell culture medium, and the rpFVIII 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.

OBIZUR is formulated as a sterile, non-pyrogenic, lyophilized powder for intravenous injection after reconstitution with the diluent (Sterile Water for Injections). OBIZUR is available in single-use vials that nominally contain 500 units (U) per vial. When reconstituted with the diluent, the product contains the following components per mL: 8.8 mg sodium chloride, 0.005mmol/mL trometamol, 1.47 mg tri-sodium citrate dehydrate, 0.15 mg calcium chloride dehydrate, 1.9 mg sucrose, and 0.05 mg polysorbate 80.

Each vial of OBIZUR is labeled 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 FVIII 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.
Composition

The composition of OBIZUR drug product is provided, see Table 1.

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Composition after reconstitution in 1 mL of SWFI</th>
<th>Function</th>
<th>Reference to Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active Substance:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Susoctocog alfa (recombinant porcine coagulation FVIII, B-domain deleted)</td>
<td>500 Units/mL (nominal)</td>
<td>Active</td>
<td>In-house Reference Standard</td>
</tr>
<tr>
<td><strong>Excipients:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polysorbate 80</td>
<td>0.0535 mg/mL</td>
<td>Stabilizer</td>
<td>NF/Ph. Eur.</td>
</tr>
<tr>
<td>Sodium chloride</td>
<td>8.765 mg/mL</td>
<td>Isotonicity/Bulking agent</td>
<td>USP/Ph. Eur.[a]</td>
</tr>
<tr>
<td>Calcium chloride dihydrate</td>
<td>0.147 mg/mL</td>
<td>Stabilizer</td>
<td>USP/Ph. Eur.</td>
</tr>
<tr>
<td>Sucrose</td>
<td>1.88 mg/mL</td>
<td>Bulking agent/Cyroprotectant</td>
<td>NF/Ph. Eur.[b]</td>
</tr>
<tr>
<td>Trometamol</td>
<td>0.005mmol/mL</td>
<td>Buffer</td>
<td>USP/Ph. Eur.</td>
</tr>
<tr>
<td>Tri-sodium citrate dihydrate</td>
<td>1.47 mg/mL</td>
<td>Buffer</td>
<td>USP/Ph. Eur.</td>
</tr>
</tbody>
</table>

a USP: United States Pharmacopoeia; Ph. Eur.: European Pharmacopoeia  
b NF: National Formulary

**PHARMACOLOGY**

**Pharmacodynamics**

Patients with acquired haemophilia A (AHA) have normal factor VIII genes but develop autoantibodies against their own factor VIII (i.e., inhibitors). These autoantibodies neutralize circulating human factor VIII and create a functional deficiency of this procoagulant protein. AHA 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 normalize the aPTT during treatment; however aPTT normalization should not be used as a measure of efficacy.

**Pharmacokinetics**

Pharmacokinetic 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 hospitalization. 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-\infty}, 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 FVIII activity data from the one-stage assays are presented as baseline-corrected values. The individual and summary PK parameters are presented in Table 2.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Individual and Summarized 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</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subject</td>
<td>Dose (U)</td>
</tr>
<tr>
<td>1</td>
<td>5000</td>
</tr>
<tr>
<td>2</td>
<td>2934</td>
</tr>
<tr>
<td>2^a</td>
<td>2934</td>
</tr>
<tr>
<td>3</td>
<td>7540</td>
</tr>
<tr>
<td>4</td>
<td>9720</td>
</tr>
<tr>
<td>5^b</td>
<td>10000</td>
</tr>
<tr>
<td>N</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>5</td>
</tr>
<tr>
<td>SD</td>
<td>1.0</td>
</tr>
</tbody>
</table>

^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-\infty} = 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.

**CLINICAL TRIALS**

The efficacy of OBIZUR for the treatment of serious bleeding episodes in subjects with acquired haemophilia 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 haemophilia A (AHA), having auto-immune inhibitory antibodies to human factor VIII, and experiencing serious bleeding episodes that required hospitalization. Subjects with a prior history of bleeding disorders other than AHA, anti-porcine factor VIII antibody titre >
20 Bethesda Units (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 AHA, 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 hemorrhage, 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 3 for definitions).

<table>
<thead>
<tr>
<th>Assessment of efficacy</th>
<th>Control of bleeding</th>
<th>Clinical Assessment</th>
<th>Factor VIII levels</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective</td>
<td>bleeding stopped</td>
<td>clinical control</td>
<td>≥50%</td>
<td>positive</td>
</tr>
<tr>
<td>Partially effective</td>
<td>bleeding reduced</td>
<td>clinical stabilization or improvement; or alternative reason for bleeding</td>
<td>≥ 20%</td>
<td>positive</td>
</tr>
<tr>
<td>Poorly effective</td>
<td>bleeding slightly reduced or unchanged</td>
<td>not clinically stable</td>
<td>&lt;50%</td>
<td>negative</td>
</tr>
<tr>
<td>Not effective</td>
<td>bleeding worsening</td>
<td>clinically deteriorating</td>
<td>&lt;20%</td>
<td>negative</td>
</tr>
</tbody>
</table>

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 anti-haemorrhagic agents prior to the first OBIZUR treatment, 16/17 (94%) had eventual treatment success reported. Eleven subjects were reported to have received anti-haemorrhagics (eg. 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 utilized 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.

INDICATIONS

OBIZUR, Anti haemophilic Factor (Recombinant), Porcine Sequence, is a recombinant DNA derived, anti-haemophilic 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 BU.

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

CONTRAINDICATIONS

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

PRECAUTIONS

Hypersensitivity Reactions

Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the injection site, chills, flushing, generalized 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 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. If such inhibitory antibodies to anti-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 Dosage and 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.

Pregnancy, Lactation and Fertility

Use in Pregnancy

Pregnancy Category B2

There are no adequate or well-controlled studies with susoctocog alfa, or other recombinant factor VIII products, in pregnant women. Studies in pregnant animals have not been conducted with susoctocog alfa. Therefore, susoctocog alfa 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.

Effects on fertility

The effects of OBIZUR on fertility have not been established.

Paediatric use

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

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

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 sections Adverse effects and 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.

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

**INTERACTIONS WITH OTHER MEDICINES**

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. 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.

**ADVERSE 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 FVIII inhibitors (≥ 0.6 Bethesda Units) that were considered an AR to OBIZUR by the investigator because treatment was discontinued after 24 hours of detection of the inhibitor.

<table>
<thead>
<tr>
<th>System Organ Class (SOC)</th>
<th>Preferred MedDRA Term (Version 17.0)</th>
<th># of ARs</th>
<th>Number of Subjects (N=29)</th>
<th>Frequency</th>
<th>% per Subject</th>
</tr>
</thead>
<tbody>
<tr>
<td>INVESTIGATIONS</td>
<td>Antibody test positive</td>
<td>2</td>
<td>2</td>
<td>Common</td>
<td>6.9%</td>
</tr>
</tbody>
</table>

Legend: ADR frequency is based upon the following scale: Very Common (≥1/10); Common (≥1/100 - <1/10), Uncommon (≥1/1,000 - <1/100), Rare (≥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 Bethesda Units (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 neutralizing 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**

No adverse reactions other than those mentioned under the above sub-heading Adverse Reactions from Clinical Trials have been observed in the post-marketing setting.

**DOSAGE AND 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 discoloration prior to administration. Do not administer if particulate matter or discoloration is found; contact Baxalta 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 4. 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 4
Dosing for Treatment of Bleeding Episodes

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

### 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 pre-filled 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 to 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 pre-filled syringe (Figure C).
7. While firmly holding the vial adapter package, connect the pre-filled 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 OBIZUR vial’s 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 pre-filled syringe and in a counterclockwise 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 discolouration 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 counterclockwise 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.

**Incompatibilities**

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

**OVERDOSAGE**

No symptoms of overdose have been reported. For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

**PRESENTATION AND STORAGE CONDITIONS**

**Nature and contents of container**

OBIZUR is available in single-use vials which contain: 500 units anti-haemophilic factor VIII (recombinant), porcine sequence (nominal).

Each pack contains one package insert and 1, 5 or 10 each of the following:

- single-use product vials
- 1 mL sterile water for injections prefilled syringes
- vial adapters with filter

**Shelf Life**

3 years.

**Storage after reconstitution**

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

**Special precautions for storage**

Store in a refrigerator (2°C – 8°C). Do not freeze. Do not use beyond the expiration date.
NAME AND ADDRESS OF THE SPONSOR

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1 Baxter Drive
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NSW 2146

POISON SCHEDULE OF THE MEDICINE

Unscheduled

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

29 April 2016

AUST R 236475

DATE OF MOST RECENT AMENDMENT

28 March 2017

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