OBIZUR 500 U powder and solvent for solution for injection

Summary of Product Characteristics Updated 04-Jan-2021 | Shire Pharmaceuticals Limited

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. Name of the medicinal product

OBIZUR 500 U powder and solvent for solution for injection

2. Qualitative and quantitative composition

Each powder vial contains nominally 500 units of B domain deleted antihaemophilic factor VIII (rDNA), porcine sequence, susoctocog alfa.

OBIZUR contains approximately 500 U/ml of susoctocog alfa after reconstitution.

The potency (U) is determined using the one-stage coagulation assay (OSCA). The specific activity of OBIZUR is approximately 10,000 U/mg protein.

OBIZUR (antihaemophilic factor VIII (rDNA), porcine sequence) is a purified protein that has 1448 amino acids with an approximate molecular mass of 175kDa.

It is produced by recombinant DNA technology in baby hamster kidney (BHK) cells. The BHK cells are cultured in media that contains foetal bovine serum. The manufacturing process is free of human serum and human protein products and does not contain any additional animal derived materials.

Excipient(s) with known effect

Each vial contains 4.6 mg (198 mM) sodium per ml of reconstituted solution.

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Powder and solvent for solution for injection.

The powder is white.

The solvent is clear and colourless.

4. Clinical particulars

4.1 Therapeutic indications

Treatment of bleeding episodes in patients with acquired haemophilia caused by antibodies to factor VIII.

OBIZUR is indicated in adults.

4.2 Posology and method of administration

Treatment with OBIZUR should be under the supervision of a physician experienced in the treatment of haemophilia.

Treatment monitoring

The product is for in-patient administration only. It requires clinical supervision of the bleeding status of the patient.

During the course of treatment, appropriate determination of factor VIII levels is advised to guide the dose to be administered and the frequency of repeated infusions. Individual patients may vary in their response to factor VIII, demonstrating different half-lives and recoveries. Dose based on bodyweight may require adjustment in underweight or overweight patients.

In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of coagulation analysis (plasma factor VIII activity) is indispensable.

When using an in vitro thromboplastin time (aPTT)-based one-stage clotting assay for determining factor VIII activity in patients' blood samples, plasma factor VIII activity results can be significantly affected by both the type of aPTT reagent and the reference standard used in the assay. Also there can be significant discrepancies between assay results obtained by aPTT-based one-stage clotting assay and the chromogenic assay according to Ph. Eur. This is of importance particularly when changing the laboratory and/or reagents used in the assay.

Posology

The dose, frequency, and duration of the therapy with OBIZUR depend on the location, extent and severity of the bleeding episode, target factor VIII activity, and on the patient´s clinical condition.

The number of units of factor VIII administered is expressed in Units (U) that are derived from an in-house standard that has been calibrated with the current World Health Organisation (WHO) standard for factor VIII products.

[no notes on this page]

One Unit (U) of factor VIII activity is equivalent to that quantity of factor VIII in one ml of normal human plasma.

The recommended initial dose is 200 U per kilogram bodyweight, given by intravenous injection (see section 6.6).

The required initial dose of OBIZUR for a patient is calculated using the following formula:

Initial dose (U/kg) ÷ Medicinal product strength (U/vial) × Body weight (kg) = Number of vials

e.g. for a 70 kg patient the number of vials for an initial dose will be calculated as follows:

200 U/kg ÷ 500 U/vial × 70 kg = 28 vials

Monitor factor VIII activity and clinical condition 30 minutes after the first injection and 3 hours after administering OBIZUR.

Monitor factor VIII activity immediately prior to and 30 minutes after subsequent doses and refer to the table below for recommended target factor VIII trough levels.

The one-stage clotting assay for factor VIII is recommended as it has been used in determination of the potency of OBIZUR and the mean recovery rate (see section 4.4 and 5.2).

The dose and frequency of administration should be based on results of factor VIII activity (to be maintained within recommended limits) and on the clinical response achieved.

Efficacy and safety data in patients with acquired haemophilia are limited (see section 5.1).

Initial phase

<table>
<tr><th>Type of bleeding</th><th>Target factor VIII trough activity (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>
<tr><td>Mild and moderate superficial muscle / no neurovascular compromise and joint bleeding</td><td>> 50%</td><td rowspan="2">200</td><td rowspan="2">Titrate subsequent doses based on clinical response and to maintain target factor VIII trough activity</td><td rowspan="2">Dose every 4 to 12 hours, frequency may be adjusted based on clinical response and measured factor VIII activity</td></tr>
<tr><td>Major moderate to severe intramuscular, retroperitoneal, gastrointestinal, intracranial bleeding</td><td>> 80%</td></tr>
</table>

Healing phase

Once bleeding has responded, usually within the first 24 hours, continue OBIZUR with a dose that maintains the trough factor VIII activity at 30-40% until bleeding is controlled. The maximum blood factor VIII activity must not exceed 200%.

The length of treatment depends on clinical judgement.

Paediatric population

The safety and efficacy of OBIZUR in children and adolescents aged below 18 years with congenital haemophilia with inhibitors or in acquired haemophilia have not yet been established. No data are available.

Method of administration

Intravenous use.

The total volume of reconstituted OBIZUR should be administered at a rate of 1 to 2 mL per minute.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance, hamster protein, or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Traceability

In order to improve traceability of biological medicinal products, the name and the batch number of the administered medicinal product should be clearly recorded.

Hypersensitivity

Allergic type hypersensitivity reactions are possible with OBIZUR. The medicinal product contains trace amounts of hamster proteins.

[no notes on this page]

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, standard medical treatment for shock should be implemented.

Inhibitors

Inhibitory antibodies against porcine factor VIII i (measured using a modification of the Nijmegen variation of the Bethesda assay) were detected before and after exposure to OBIZUR. Inhibitor titres of up to 29 Bethesda units were recorded at baseline yet patients responded positively to OBIZUR. It is recommended that treatment should be based on clinical judgement and not based on detection of inhibitory antibodies by the Bethesda assay. Anamnestic reactions with rise in human factor VIII and/or porcine factor VIII inhibitors have also been reported in patients treated with OBIZUR. These anamnestic rises may result in lack of response to OBIZUR.

There is a lack of clinical information on the development of inhibitory antibodies to OBIZUR following repeated administration. Therefore, OBIZUR must only be administered when considered clinically necessary. Extensive cutaneous purpura do not necessarily require treatment.

OBIZUR is produced by recombinant DNA technology in baby hamster kidney cells. Antibodies to baby hamster kidney cell protein were not detected in patients after exposure to OBIZUR.

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.

If venous catheterisation is required, the risk of catheter-related complications such as catheter site thrombosis should be considered.

Factor VIII activity determined by the chromogenic assay is generally lower than factor VIII activity determined by the one-stage clotting assay. Measurement of factor VIII activity must always be carried out using the same assay methodology on any one patient. The one-stage assay is recommended because it has been used in determination of the potency and the mean recovery rate of OBIZUR (see sections 4.2 and 5.2).

Cardiovascular events

In patients with existing cardiovascular risk factors, substitution therapy with FVIII may increase the cardiovascular risk.

Sodium content

OBIZUR contains 4.6 mg sodium in 1 mL of reconstituted solution in each vial, equivalent to 0.23% of the WHO recommended maximum daily intake of 2 g sodium for an adult. Multiple vials must be taken per dose.

e.g A 70 kg patient using the recommended 200 U/kg dose would require 28 vials which results in a sodium intake of 128.8 mg per treatment. This is equivalent to 6.44% of the WHO recommended maximum daily intake of 2 g of sodium for an adult.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions of OBIZUR with other medicinal products have been reported.

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with OBIZUR. Experience regarding the use of OBIZUR during pregnancy and breast-feeding is not available. Therefore, OBIZUR should be used during pregnancy and lactation only if clearly indicated.

4.7 Effects on ability to drive and use machines

OBIZUR has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile:

Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the injection site, chills, flushing, generalized urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) are possible and may progress to severe anaphylaxis (including shock) (see section 4.4).

Patients with acquired haemophilia may develop inhibitory antibodies to porcine factor VIII. Inhibitory antibodies, including anamnestic responses, may result in a lack of response to OBIZUR.

Tabulated list of adverse reactions:

The table presented below is according to the MedDRA system organ classification (SOC and preferred term level). In the clinical study of OBIZUR for acquired haemophilia, 29 adult patients were evaluable for safety.

[no notes on this page]

Frequencies have been evaluated according to the following convention: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

System organ class	Adverse reaction	Frequency
Investigations	Positive test for inhibitory antibodies against porcine factor VIII (see section 4.4)	Common
Immune System Disorders	Anamnestic Reaction	Very common

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 via the Yellow Card Scheme Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

The effects of higher than recommended doses of OBIZUR have not been characterised.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihaemorrhagics, blood coagulation factors. ATC code: B02BD14

Mechanism of action

Obizur is a recombinant, B-domain deleted, porcine sequence factor VIII (susoctocog alfa). It is a glycoprotein.

Immediately after release in the patient's circulation, factor VIII binds to von Willebrand factor (vWF). The factor VIII/von Willebrand factor complex consists of two molecules (factor VIII and von Willebrand factor) with different physiological functions. Activated factor VIII acts as a co-factor for activated factor IX, accelerating the conversion of factor X to activated factor X, which ultimately converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed.

Acquired haemophilia is a rare bleeding disorder in which patients with normal factor VIII genes develop inhibitory autoantibodies directed against factor VIII. These autoantibodies neutralise circulating human factor VIII thus creating a deficiency of available factor VIII. Circulating antibodies (inhibitors) targeted against human factor VIII have minimal or no cross reactivity against OBIZUR.

OBIZUR temporarily replaces the inhibited endogenous factor VIII that is needed for effective haemostasis.

Clinical efficacy and safety

The safety and efficacy of OBIZUR for the treatment of serious bleeding episodes in patients with acquired haemophilia with autoimmune inhibitory antibodies to human factor VIII was investigated in a prospective, non-randomised, open-label study of 28 patients (18 caucasian, 6 black, and 4 asian). The study included patients presenting with life and / or limb threatening bleeding requiring hospitalisation.

All initial bleeding episodes had a positive response to treatment at 24 hours after initial dosing as assessed by the primary investigator. A positive response was one where bleeding had stopped or was reduced, with clinical improvement or with factor VIII activity above a pre-specified target.

A positive response was observed in 95% (19/20) of patients 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 control (resolution) of the initial bleeding episode. Of those patients 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 patients were reported to have received anti-haemorrhagic agents (e.g. rFVIIa, activated prothrombin-complex concentrate, tranexamic acid) prior to first treatment with OBIZUR. Of these 11patients, eight had eventual successful treatment (73%).

The median dose per injection to successfully treat the primary bleed was 133 U/kg and the median total dose was 1523 U/kg for a median of 6 days. The median number of daily infusions per patient was 1.76 (range: 0.2 to 5.6). In the initial 24 hour period, the median total dose of 493 U/kg were utilised in the clinical study with a median of 3 infusions. When treatment was required beyond 24 hours, a median total dose of 1050 U/kg were utilized with a median of 10.5 infusions (median dose 100 U/kg) to control a bleeding episode.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with OBIZUR in all subsets of the paediatric population in treatment of acquired haemophilia (see section 4.2 for information on paediatric use).

[no notes on this page]

This medicinal product has been authorised under 'exceptional circumstances'. This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product.

The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Pharmacokinetic data from 5 patients with acquired haemophilia whilst in a non-bleeding state are presented in Table 1.

Table 1 : Individual pharmacokinetic data for factor VIII activity after administration of the final dose of OBIZUR to 5 patients with acquired haemophilia. Patients were in a non-bleeding state. Factor VIII activity was measured by the one-stage clotting assay.

Patient	Dose (U)	Dose (U/kg)	Baseline hFVIII activity (%)	t½ (h)	Tmax (h)	Amax (%)	AUC0-t (%·t)	AUC0-∞ (%·t)
1	5000	76.7	89	17	0.42	213	3124	4988
2	2934	30.0	18	4.6	0.42	100	694	712
3	7540	144.2	3	5.3	0.45	74	473	492
4	9720	206.8	0	1.8	0.50	53	122	135
5	10000	133.3	N/A	4.2	0.75	178	1583	1686

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; $t_{½}$ = terminal half-life; T_{max} = time of maximum observed % activity, N/A = not available.

The mean recovery rate after the initial dose of 200 U/kg was 1.06 ± 0.75 U/ml per U/kg (range 0.10-2.61) measured with the one-stage coagulation assay.

Although factor VIII activity determined by the chromogenic assay is generally lower than the factor VIII activity determined by the one-stage clotting assay, post-infusion factor VIII activities in patients with acquired haemophilia in clinical study OBI-1-301 tended to be higher when determined with the chromogenic assay than with the one-stage clotting assay (see section 4.4).

Inhibitory antibodies against OBIZUR were measured using a modification of the Nijmegen variation of the Bethesda assay method. Three patients included in pharmacokinetic analysis had a detectable anti-porcine factor VIII inhibitor titre at baseline (≥ 0.6 Bethesda Units (BU)/mL). Three of the five patients had no detectable anti-porcine factor VIII titres post-treatment (< 0.6 BU/mL based on the last reported result), two patients had a detectable anti-porcine factor VIII titre (≥ 0.6 BU/mL).

The mean half-life of OBIZUR in nine evaluable patients in the bleeding state was (about) 10 hours (range 2.6 to 28.6 hours).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology or repeated dose toxicity. However, in repeated dose toxicity studies, the incidence and severity of glomerulopathy observed in monkeys intravenously administered OBIZUR at doses of 75, 225 and 750 U/kg/day tended to increase over time.

Animal reproduction studies have not been conducted with OBIZUR.

6. Pharmaceutical particulars

6.1 List of excipients

Powder

Polysorbate 80

Sodium chloride

Calcium chloride dihydrate

Sucrose

Trometamol hydrochloride

Sodium citrate

Solvent

[no notes on this page]

Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

30 months.

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

6.4 Special precautions for storage

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

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

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

• powder vials (type I glass) with a stopper (butyl rubber coated with FluroTec®) and a flip-off seal;

• pre-filled (type I glass) syringes with a stopper (bromobutyl rubber coated with FluroTec® foil on the contact side), a bromobutyl rubber tip cap and a Luer lock adapter;

• fluid transfer device with an integral plastic spike.

6.6 Special precautions for disposal and other handling

After reconstitution, the solution is clear, colourless, free from particles and has a pH of 6.8 to 7.2. The osmolality of the formulation buffer ranges between 59 and 65 10% mOsm/kg H2O.

Reconstituted medicinal product should be inspected visually for particulate matter and discolouration prior to administration. Solutions with particles or discolouration must not be administered.

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

Preparation

Before starting reconstitution you will need the following:

• Calculated number of powder vials;

• Same number of 1 mL solvent syringes and sterile vial adapters;

• Alcohol swabs;

• Large sterile syringe to contain the final volume of reconstituted product.

The procedures below are provided as general guidelines for the preparation and reconstitution of OBIZUR. Repeat following reconstitution instructions for each powder vial to be reconstituted.

Reconstitution

Use aseptic technique during the reconstitution procedure.

1. Bring the OBIZUR powder vial and the pre-filled solvent syringe to room temperature.

2. Remove the plastic cap from the OBIZUR powder 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 centre of the vial adapter. Do not remove the vial adapter from the 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 solvent syringe (**figure C**).

7. While firmly holding the vial adapter package connect the pre-filled solvent syringe to the vial adapter by pushing the syringe tip down onto the Luer lock in the centre 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 powder vial on a clean, flat, hard surface. Place the vial adapter over the OBIZUR powder vial and firmly push the filter spike of the vial adapter through the centre of the OBIZUR powder 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 powder vial.

[no notes on this page]

11. Gently swirl (in a circular motion) the OBIZUR powder vial without removing the syringe until all of the powder is fully dissolved /reconstituted (**figure G**). The reconstituted solution should be inspected visually for particulate matter before administration. Do not use if particulate matter or discolouration 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 solvent syringe and in a counterclockwise motion unscrew the syringe from the vial adapter (**figure H**).

13. Use OBIZUR immediately and within 3 hours after reconstitution when stored at room temperature.

Figure A

Figure B

Figure C

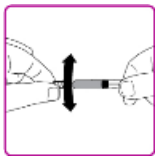


Figure D

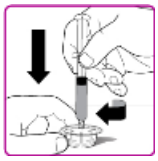


Figure E

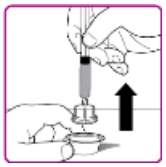


Figure F

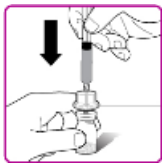
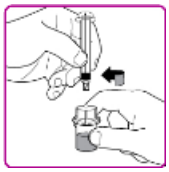


Figure G

Figure H



Administration

For intravenous injection only.

• Inspect the reconstituted OBIZUR solution for particulate matter and discolouration 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 injection.

Using aseptic technique, administer using the following procedure:

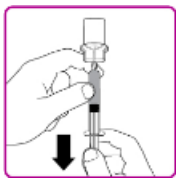
1. Once all vials have been reconstituted, connect a large syringe to the vial adapter by gently pushing the syringe tip down onto the Luer lock in the centre of the vial adapter, and turning clockwise until the syringe is secured.

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.

Figure I



7. Marketing authorisation holder

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8. Marketing authorisation number(s)

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9. Date of first authorisation/renewal of the authorisation

[no notes on this page]

Date of first authorisation: 11 November 2015

Date of latest renewal: 16 November 2020

10. Date of revision of the text

16 November 2020

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

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