

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use OBIZUR safely and effectively. See full prescribing information for OBIZUR.

OBIZUR [Antihemophilic Factor (Recombinant), Porcine Sequence] Lyophilized Powder for Solution For Intravenous Injection

Initial U.S. Approval: 2014

INDICATIONS AND USAGE

OBIZUR, Antihemophilic Factor (Recombinant), Porcine Sequence, is an antihemophilic factor indicated for the treatment of bleeding episodes in adults with acquired hemophilia A. (1)

Limitations of Use:

- Safety and efficacy of OBIZUR has not been established in patients with a baseline anti-porcine factor VIII inhibitor titer of greater than 20 BU. (1)
- OBIZUR is not indicated for the treatment of congenital hemophilia A or von Willebrand disease. (1)

DOSAGE AND ADMINISTRATION

For intravenous use after reconstitution only (2)

- Initial dose of OBIZUR is 200 units per kg. (2.1)
- Titrate dose and frequency of administration based on factor VIII recovery levels and individual clinical response. (2.1)

DOSAGE FORMS AND STRENGTHS

OBIZUR is available as lyophilized powder for solution in single-use vials containing nominally 500 units per vial. (3)

CONTRAINDICATIONS

Do not use in patients who have had life-threatening hypersensitivity reactions to OBIZUR or its components, including hamster protein. (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity reactions, including anaphylaxis, may occur. Should symptoms occur, discontinue OBIZUR and administer appropriate treatment. (5.1)
- Development of inhibitory antibodies to OBIZUR has occurred. If expected plasma factor VIII activity levels are not attained, or if bleeding is not controlled with an appropriate dose, perform an assay that measures porcine factor VIII inhibitor concentration. (5.2)

ADVERSE REACTIONS

Common adverse reaction observed in greater than 5% of subjects in the clinical trial were development of inhibitors to porcine factor VIII. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Baxter Healthcare Corporation at 1-866-888-2472 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Pregnancy: No human or animal data. Use only if clinically needed. (8.1)

See 17 for PATIENT COUNSELING INFORMATION.

Revised: 10/2014

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

- 2.1 Dose
- 2.2 Reconstitution
- 2.3 Administration

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

- 5.1 Hypersensitivity Reactions
- 5.2 Inhibitory Antibodies
- 5.3 Monitoring Laboratory Tests

6 ADVERSE REACTIONS

- 6.1 Clinical Trial Experience

8 USE IN SPECIFIC POPULATIONS

- 8.1 Pregnancy
- 8.3 Nursing Mothers
- 8.4 Pediatric Use
- 8.5 Geriatric Use

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

- 12.1 Mechanism of Action
- 12.2 Pharmacodynamics

13 NONCLINICAL TOXICOLOGY

- 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

14 CLINICAL STUDIES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

OBIZUR, Antihemophilic Factor (Recombinant), Porcine Sequence, is a recombinant DNA derived, antihemophilic factor indicated for the treatment of bleeding episodes in adults with acquired hemophilia A.

Limitations of Use:

- Safety and efficacy of OBIZUR has not been established in patients with baseline anti-porcine factor VIII inhibitor titer greater than 20 BU.
- OBIZUR is not indicated for the treatment of congenital hemophilia A or von Willebrand disease.

2 DOSAGE AND ADMINISTRATION

For intravenous use after reconstitution only

2.1 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 and prevention 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.

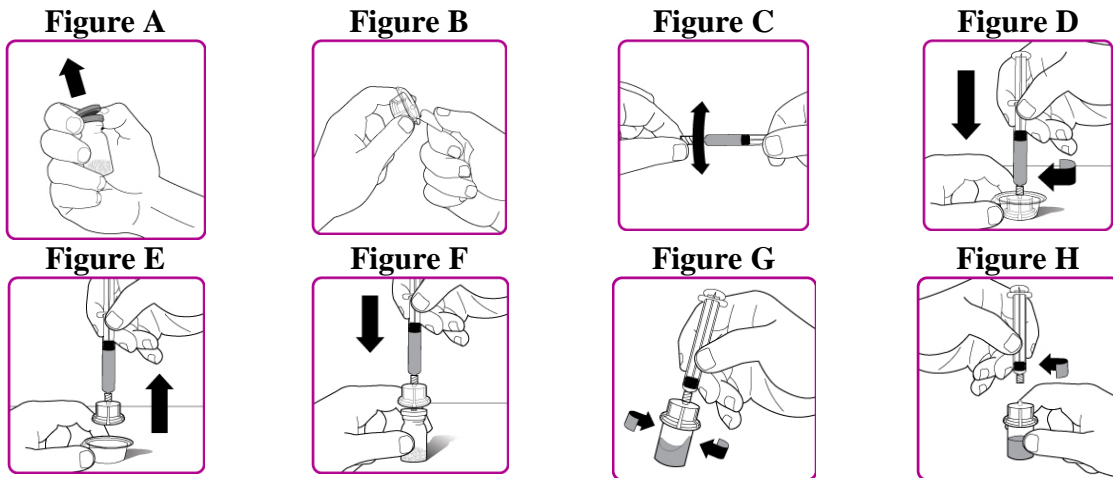
Table 1
Dosing for Treatment of Bleeding Episodes

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)			

2.2 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 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.



2.3 Administration

For intravenous injection only

- Inspect the reconstituted OBIZUR solution for particulate matter and discoloration prior to administration. The solution should be clear and colorless 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).

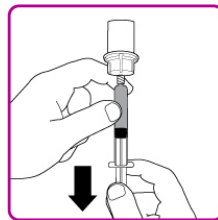


Figure I

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.

3 DOSAGE FORMS AND STRENGTHS

OBIZUR is available as a white lyophilized powder in single-use glass vials containing nominally 500 units per vial.

4 CONTRAINDICATIONS

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

5 WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Hypersensitivity reactions can occur with OBIZUR. OBIZUR contains trace amounts of hamster proteins. Early signs of allergic reactions, which can progress to anaphylaxis, include angioedema, chest-tightness, dyspnea, hypotension, wheezing, urticaria, and pruritus. Immediately discontinue administration and initiate appropriate treatment if allergic or anaphylactic-type reactions occur.

5.2 Inhibitory Antibodies

Inhibitory antibodies to OBIZUR have occurred. Monitor patients for the development of antibodies to OBIZUR by appropriate assays [see *Monitoring Laboratory Tests (5.3)*]. 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.

5.3 Monitoring Laboratory Tests

- Perform one-stage clotting assay to confirm that adequate factor VIII levels have been achieved and maintained [see *Dosage and Administration (2)*].
 - 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.

6 ADVERSE REACTIONS

Common adverse reactions observed in greater than 5% of subjects in the clinical trial were development of inhibitors to porcine factor VIII.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction (AR) rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The safety and efficacy of OBIZUR was evaluated in a multi-center, prospective, open-label, clinical trial that investigated adult patients with acquired hemophilia A. Twenty-nine adult subjects were enrolled in the study, received at least one dose of OBIZUR and were evaluable for safety [see *Clinical Studies (14)*]. Of the 29 adult subjects, 10 were between

the ages of 40 and 65, and 19 were 65 years of age or older (18 Caucasian, 6 African-American, and 5 Asian). Ten (34%) subjects were female.

The most frequently reported adverse reaction in patients with acquired hemophilia A was the development of inhibitors to porcine factor VIII.

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 titer 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 titer and eight (80%) experienced a decreasing to a non-detectable titer.

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.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Animal reproduction studies have not been conducted with OBIZUR. It is also not known whether OBIZUR can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. OBIZUR should be given to a pregnant woman only if clearly needed.

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

8.5 Geriatric Use

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 *Adverse Reactions* (6) and *Clinical Studies* (14)]. 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.

11 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, 0.04 mg Tris-base, 0.73 mg Tris-HCl, 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 U 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.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

OBIZUR temporarily replaces the inhibited endogenous factor VIII that is needed for effective hemostasis in patients with acquired hemophilia A.

12.2 Pharmacodynamics

Patients with acquired hemophilia 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.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies in animals to evaluate the carcinogenic potential of OBIZUR, or studies to determine genotoxicity and the effects of OBIZUR on fertility, have not been performed.

14 CLINICAL STUDIES

The efficacy of OBIZUR for the treatment of serious bleeding episodes in subjects with acquired hemophilia 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 hemophilia 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 titer > 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. Hemostatic 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 2 for definitions).

Assessment of efficacy	Control of bleeding	Clinical Assessment	Factor VIII levels	Response
Effective	bleeding stopped	clinical control	≥50%	positive
Partially effective	bleeding reduced	clinical stabilization 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 anti-hemorrhagic agents prior to the first OBIZUR treatment, 16/17 (94%) had eventual treatment success reported. Eleven subjects were reported to have received anti-hemorrhagics (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.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

OBIZUR is supplied as a white lyophilized powder in single-use vials in the following package sizes:

Nominal Strength	Package Size	Kit NDC
500 units	1-vial package	0944-5001-01
500 units	5-vial package	0944-5001-05
500 units	10-vial package	0944-5001-10

Each package contains one package insert and appropriate number of each of the components listed below correlating to the vial package size:

- Single-use vial of OBIZUR [NDC 0944-5011-01]
- Pre-filled syringe with 1 mL Sterile Water for Injection [NDC 0944-0011-01]
- Vial adapter with filter

The actual amount of OBIZUR in units is stated on the label of each vial.

Storage and Handling

- **Store OBIZUR at refrigeration temperature of 2° to 8°C [36° to 46°F].** Do not freeze.
- Store vials in the original package to protect from light.
- Do not use beyond the expiration date printed on the carton or vial.
- Use OBIZUR within 3 hours after reconstitution. Discard any unused reconstituted product if not used within 3 hours after reconstitution.
- Do not use OBIZUR if the reconstituted solution is cloudy or has particulate matter.

17 PATIENT COUNSELING INFORMATION

- Advise patients to report any adverse reactions or problems following OBIZUR administration to their physician or healthcare provider.

Baxter and Obizur are trademarks of Baxter International Inc., registered in the U.S. Patent and Trademark Office.

Manufactured by:

Baxter Healthcare Corporation
Westlake Village, CA 91362 USA
U.S. License No. 140