INDICATIONS AND USAGE
ALTUVIIIO (antihemophilic factor [recombinant], Fc-VWF-XTEN fusion protein-ehlt), lyophilized powder for solution, for intravenous use

Limitation of Use:

ALTUVIIIO is not indicated for the treatment of von Willebrand disease. (1)

For in intravenous use only:

Each ALTUVIIIO vial label states Factor VIII activity in international units (IU or unit). (2.1)

For routine prophylaxis: 50 IU/kg once weekly. (2.1)

For on-demand treatment and control of bleeding episodes and perioperative management: 50 IU/kg (2.1)

Estimated Increment of Factor VIII (IU/dL or % of normal) = 50 IU/kg × 2 (IU/dL per IU/kg) (2.1)

To achieve a specific target Factor VIII activity level, use the following formula: Dosage (IU) = Body Weight (kg) × Desired Factor VIII Increase (IU/dL or % normal) × 0.5 (IU/kg per IU/dL). (2.1)

Dosage and Administration

For routine prophylaxis for adults and children with hemophilia A (congenital factor VIII deficiency) for:

ALTUVIIIO [antihemophilic factor (recombinant), Fc-VWF-XTEN fusion protein-ehlt], lyophilized powder for solution, for intravenous use

Initial U.S. Approval: 2023

DOSAGE FORMS AND STRENGTHS

For injection: nominally 250, 500, 750, 1000, 2000, or 4000 IU, lyophilized powder in single-dose vials for reconstitution. (3)

CONTRAINDICATIONS

Do not use in patients who have had severe hypersensitivity reactions, including anaphylaxis, to ALTUVIIIO or excipients of ALTUVIIIO. (4)

WARNINGS AND PRECAUTIONS

- Hypersensitivity reactions, including anaphylaxis, may occur. Should symptoms occur, immediately discontinue ALTUVIIIO and initiate appropriate treatment. (5.1)

- Neutralizing antibodies (inhibitors) to Factor VIII have been reported. 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 Factor VIII inhibitor concentration. (5.2, 5.3)

ADVERSE REACTIONS

Most common adverse reaction (incidence >10%) are headache and arthralgia. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Bioverativ Therapeutics Inc. (A SANGIIFI COMPANY) at 1-800-633-1610 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

Pediatric Use: No dosing adjustment is needed in this population. (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 02/2023

Table 1: Dosing for On-demand Treatment and Control of Bleeding Episodes

<table>
<thead>
<tr>
<th>Type of Bleeding</th>
<th>Recommended Dose</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor and Moderate</td>
<td>For example: uncomplicated joint bleeds, minor muscular bleeds, mucosal or subcutaneous bleeds</td>
<td>Single dose of 50 IU/kg</td>
</tr>
<tr>
<td>Major</td>
<td>For example: Intracranial, retroperitoneal, iatrogenic and neck bleeds, muscle bleeds with compartment syndrome, and bleeds associated with a significant decrease in the hemoglobin level</td>
<td>Single dose of 50 IU/kg</td>
</tr>
</tbody>
</table>

For resumption of prophylaxis (if applicable) after treatment of a bleed, it is recommended to allow an interval of at least 72 hours between the last 50 IU/kg dose for treatment of a bleed and resuming prophylaxis dosing. Thereafter, prophylaxis can be continued as usual on the patient’s regular schedule.

Perioperative Management

ALTUVIIIO dosing for perioperative management is provided in Table 2.
2.2 Preparation and Reconstitution

1. Use aseptic technique and a flat work surface during the reconstitution procedure.

2. Allow the ALTUVIIIO vial, containing the white to off-white lyophilized powder, and the prefilled diluent syringe to reach room temperature before use.

3. Remove the plastic cap from the ALTUVIIIO vial and wipe the rubber stopper of the vial with an alcohol wipe. Allow the rubber stopper to dry.

4. Completely remove the backing from the vial adapter package by peeling back the lid. Do not remove the vial adapter from the package or touch the inside of the package of the adapter.

5. Keep the vial on a flat surface. Hold the vial with one hand and using the other hand, place the vial adapter in its package over the vial. The spike should be placed directly above the center of the rubber stopper. Push the vial adapter straight down until the spike on the vial adapter punctures the center of the vial stopper and is fully inserted.

6. Lift the package cover away from the vial adapter and throw away the cover.

7. Only use the prefilled diluent syringe provided to reconstitute the powdered medicine. Hold the plunger rod by the circular disk. Place the tip of the plunger rod into the end of the prefilled diluent syringe. Turn the plunger rod to the right until it is firmly attached.

8. With one hand, hold the prefilled diluent syringe directly under the cap with the cap pointing up. Make sure you are holding the prefilled diluent syringe by the ridged part directly under the cap. Do not use if the cap has been removed or is not securely attached.

9. With your other hand, grasp the cap and bend it at a 90 degree angle until it snaps off. After the cap snaps off, you will see the glass tip of the prefilled diluent syringe. Do not touch the glass tip of the prefilled diluent syringe or the inside of the cap.

10. Be sure the vial is sitting on a flat surface. Insert the tip of the prefilled diluent syringe into the vial adapter opening. Turn the prefilled diluent syringe to the right until it is securely attached to the vial adapter.

11. Slowly push down on the plunger rod to inject all of the liquid (diluent) from the prefilled diluent syringe into the vial. The plunger rod may rise slightly afterward. This is normal.

12. With the prefilled diluent syringe still connected to the adapter, gently swirl the vial until the powder is completely dissolved. Check the solution through the vial to make sure the powder is fully dissolved. The solution should look clear and colorless to colorless ambient. Do not shake. Do not use the reconstituted ALTUVIIIO if it contains visible particles or is cloudy.

13. POOLING: pooling is the process of combining two or more reconstituted vials into a larger luer lock syringe (not provided in the carton). If the dose requires more than one vial, reconstitute each vial as described above (See Steps 3–12) with the prefilled diluent syringe provided. Do not detach the prefilled diluent syringe until you are ready to attach the large luer lock syringe to the next vial. Keep the vial adapter attached to the vial as you will need it for attaching a large luer lock syringe. Use a larger luer lock plastic syringe to combine the contents of the reconstituted vials into the syringe, similar as described in the Steps 13–14. Repeat this pooling procedure with each vial you will be using. Once you have pooled the required dose, proceed with the administration steps using the larger luer lock syringe.

14. Make sure the plunger rod is pressed all the way down and the diluent syringe is firmly attached to the vial adapter. Turn the vial upside-down. Slowly turn down on the plunger rod to draw all the solution from the vial into the diluent syringe. Be careful not to pull the plunger rod completely out of the diluent syringe.

15. Gently unscrew the diluent syringe from the vial adapter by turning it to the right. Dispose of the vial with the adapter still attached. If you are not ready to inject, put the cap on the syringe carefully back onto the syringe tip. Do not touch the syringe tip or the inside of the cap.

16. Use the reconstituted ALTUVIIIO as soon as possible, but no later than 3 hours after reconstitution. Do not touch the glass tip of the syringe if not used immediately after reconstitution. Protect from direct sunlight. Do not refrigerate after reconstitution.

2.3 Administration

For intravenous use only.

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use ALTUVIIIO solution if particulate matter or discoloration is observed.
- Do not administer reconstituted ALTUVIIIO in the same tubing with other medications.

Administration Steps:

1. Attach the syringe to the connector end of the infusion set tubing by turning it to the right until it is securely attached.

2. Push the plunger rod until all air is removed from the syringe and ALTUVIIIO has filled the infusion set needle. Do not push ALTUVIIIO solution through the needle.

3. Remove the protective needle cover from the infusion set needle.

4. Perform intravenous injection. The rate of administration should be determined by the patient’s comfort level and no faster than:

   - For adults and adolescents: 1–2 minutes per vial.
   - For children: 2–3 minutes per vial if body weight is greater than or equal to 20 kg; or 6 minutes per vial if body weight is less than 20 kg.

5. After infusing ALTUVIIIO, remove and properly discard the infusion set.

3. DOSAGE FORMS AND STRENGTHS

ALTUVIIIO is available as a white to off-white lyophilized powder for reconstitution in single-dose vials containing nominally 250, 500, 750, 1000, 2000, 3000, or 4000 international units (IU) per vial.

4. CONTRAINDICATIONS

ALTUVIIIO is contraindicated in patients who have had severe hypersensitivity reactions, including anaphylaxis, to the product or its excipients [see Description (11)].

5. WARNINGS AND PRECAUTIONS

5.1 Hypersensitivity Reactions

Allergic-type hypersensitivity reactions, including anaphylaxis, may occur with ALTUVIIIO. Allergic-type hypersensitivity reactions were not reported in the clinical trials. Inform patients of signs of hypersensitivity reactions that may progress to anaphylaxis (including hives, shortness of breath, chest tightness, wheezing, hypotension and itching). Advise patients to discontinue use of ALTUVIIIO if hypersensitivity symptoms occur and contact a physician and/or seek immediate emergency care.

5.2 Neutralizing Antibodies

Formation of neutralizing antibodies (inhibitors) to Factor VIII are possible following administration of ALTUVIIIO. Neutralizing antibodies were not reported in the clinical trials. Monitor all patients for the development of Factor VIII inhibitors by appropriate clinical observations and laboratory tests. If the patient’s plasma Factor VIII level falls to zero as expected or if bleeding is not controlled after ALTUVIIIO administration, the presence of an inhibitor (neutralizing antibodies) should be suspected, and appropriate testing performed [see Warnings and Precautions (5.3)].

5.3 Monitoring Laboratory Tests

If assessment of plasma Factor VIII activity is needed, it is recommended to use a validated one-stage clotting assay [see Dosage and Administration (2)]. The ALTUVIIIO Factor VIII activity level is overestimated by the chromogenic assay and a specific allergic acid based aPTT reagent in one-stage clotting assay by approximately 2.5-fold. If these assays are used, divide the result by 2.5 to approximate the patient’s ALTUVIIIO Factor VIII activity level. Use of a reference laboratory is recommended when a qualified one-stage clotting assay or chromogenic assay is not available locally. Monitor for the development of Factor VIII inhibitors. If bleeding is not controlled with ALTUVIIIO and the expected factor VIII activity plasma levels are not attained, perform an assay to determine if Factor VIII inhibitors are present (use Bethesda Units to titrate inhibitors).

6. ADVERSE REACTIONS

The most common adverse reactions (>10% of subjects) reported in clinical trials were headache and arthralgia.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction 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 practice.

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Table 2: Dosing for Perioperative Management

<table>
<thead>
<tr>
<th>Type of Surgery</th>
<th>Pre-operative Dose</th>
<th>Post-operative Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor</td>
<td>Single dose of 50 IU/kg</td>
<td>An additional dose of 30 or 50 IU/kg after 2 to 3 days may be considered.</td>
</tr>
<tr>
<td>Major</td>
<td>Single dose of 50 IU/kg</td>
<td>Additional doses of 30 or 50 IU/kg every 2 to 3 days may be administered as clinically needed for perioperative management.</td>
</tr>
</tbody>
</table>
The safety of ALTUVIIIO has been evaluated in 158 previously treated patients (PTPs) (134 adults and 25 adolescents) with severe Hemophilia A (<1% endogenous FVIII activity or a genetic mutation consistent with severe Hemophilia A) who received at least one dose of ALTUVIIIO for either routine prophylaxis, on-demand treatment of bleeding episodes or perioperative management. A total of 152 (96%) subjects achieved at least 25 exposure days and 115 (72%) subjects achieved at least 50 exposure days with a median of 53.0 (range 2-63) for both exposure and injections per subject. Overall exposure was monitored for a total of 151.5 subject-years. Adverse drug reactions (ADRs) (summarized in Table 3) were reported in 57 (36%) of the 159 subjects treated with routine prophylaxis or on-demand therapy. There were no age-specific differences in ADRs observed between adolescent and adult subjects. In the study, no inhibitors were detected and no ADRs of anaphylaxis were reported.

### Table 3: Adverse Drug Reactions with Frequency of ≥3% Reported for ALTUVIIIO

<table>
<thead>
<tr>
<th>MedDRA System Organ Class</th>
<th>Adverse Drug Reactions</th>
<th>Number of Subjects n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nervous system disorders</td>
<td>Headache</td>
<td>33 (21)</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Arthralgia</td>
<td>26 (16)</td>
</tr>
<tr>
<td></td>
<td>Back pain</td>
<td>9 (6)</td>
</tr>
</tbody>
</table>

*includes preferred terms of headache (32 subjects) and migraine (1 subject).

In the ongoing pediatric study, the safety of ALTUVIIIO was evaluated in 67 male PTPs <12 years of age with severe Hemophilia A who received at least one dose of ALTUVIIIO. At the time of the interim analysis, a total of 23 (34%) subjects achieved at least 25 exposure days with a median of 14.0 (range 1-46) for both exposure days and injections per subject.

Adverse drug reactions, headache, were reported in 1 (1%) of subjects. In the study, no inhibitors were detected and no ADRs of anaphylaxis were reported.

Thromboembolic events occurred in 1% (3/206) of subjects in the long term safety extension study; these three subjects had pre-existing risk factors.

Immunogenicity:
No subjects developed neutralizing antibodies towards human von Willebrand factor (VWF).
No subjects developed neutralizing antibodies to Factor VIII [see immunogenicity (12.6)].

### 8 USE IN SPECIFIC POPULATIONS

#### 8.1 Pregnancy

**Risk Summary**

There are no data with ALTUVIIIO use in pregnant women to inform a drug-associated risk. Animal developmental and reproductive studies have not been conducted with ALTUVIIIO. Therefore, it is not known whether ALTUVIIIO can affect reproductive capacity or cause fetal harm when given to pregnant women.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

#### 8.2 Lactation

**Risk Summary**

There is no information regarding the presence of ALTUVIIIO in human milk, its effects on the breastfed infant, or its effects on milk production. The development and health benefits of breastfeeding should be considered along with the mother’s clinical need for ALTUVIIIO and any potential adverse effects on the breastfed infant from ALTUVIIIO or from the underlying maternal condition.

#### 8.4 Pediatric Use

**Safety, efficacy, and pharmacokinetics (PK) have been evaluated in 92 previously treated, pediatric patients <18 years of age who received at least one dose of ALTUVIIIO as part of routine prophylaxis, treatment of bleeding episodes, or perioperative management. Adolescent subjects were enrolled in the adult and adolescent study and pediatric subjects <12 years of age were enrolled in an ongoing pediatric trial. Thirty-one subjects (33.7%) were <6 years of age, 36 (39.1%) subjects were 6 to <12 years of age, and 25 subjects (27.2%) were adolescents (12 to ≤18 years of age). Interim data from a pediatric study of the 67 subjects <12 years of age that showed no dosing adjustment was required [see Clinical Pharmacology (12.3)].

**Geriatric Use**

Clinical studies of ALTUVIIIO did not include sufficient numbers of subjects 65 years of age and older to determine whether or not they respond differently from younger subjects. However, clinical experience with other Factor VIII products has not identified differences between the elderly and younger patients.

#### 11 DESCRIPTION

ALTUVIIIO [antihemophilic factor (recombinant), Fc-VWF:XTEN fusion protein-eH] is a sterile, non-pyrogenic, white to off-white lyophilized powder for reconstitution for intravenous injection. The active ingredient in ALTUVIIIO is a fully recombinant fusion protein comprising a single chain B-domain deleted (BDD) analogue of human FVIII covalently fused to the Fc domain of human immunoglobulin G1 (IgG1), the FVIII-binding D’D3 domain of human von Willebrand factor (VWF), and two XTEN polypeptides. ALTUVIIIO contains 2829 amino acids with an apparent molecular weight of 312 kDa. ALTUVIIIO is synthesized as 2 polypeptide chains that are covalently linked by 2 Fc hinge disulfide bonds. The first FVIII-XTEN-Fc polypeptide chain contains the A1A2 domain of FVIII along with 5 amino acids from B-domain (1-745 amino acids) fused to the 28KTEN polypeptide (in place of the natural FVIII B-domain), the A3C12 domain of FVIII (1649-2332), and the Fc domain of human IgG1. The second WVF-XTEN-a2-Fc polypeptide chain contains the D’D3 domain of WVF (1-477 amino acids) fused to the 14E6 polypeptide, a thrombin cleavable acidic region 2 sequence from FVIII and the Fc domain of human IgG1. The Fc domain includes the hinge, CH1, and CH2 domains of IgG1. The Fc, Wf, and XE1TEN portions of the molecule extend the half-life of ALTUVIIIO in plasma. ALTUVIIIO is produced by recombinant DNA technology in a human embryonic kidney (HEK) cell line, which has been extensively characterized. ALTUVIIIO is manufactured without addition of human- or animal-derived components and purified by a combination of multiple chromatography steps, a removal of endotoxin step, a polishing step for viral clearance, and ultrafiltration steps.
The ongoing pediatric study enrolled 67 male PTPs were evaluable for efficacy. A total of 149 subjects (93.7%) completed the study. Subjects were aged 12 to 72 years and included 25 adolescent subjects undergoing major or minor surgical procedures. During treatment (up to 49.64 weeks) in the clinical studies, 1/277 (2.2%) of ALTVIIIO patients developed anti-drug antibodies. No impact of ADAs on the FVIIlll activity-time profiles and PK exposure parameters was observed. No impact of ADAs with respect to bleeding episodes and in the pharmacodynamic response was noted.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

No carcinogenicity or mutagenicity studies have been conducted with ALTVIIIO. No studies have been conducted to evaluate the effects of ALTVIIIO on fertility.

14 CLINICAL STUDIES

The safety, efficacy, and pharmacokinetics of ALTVIIIO were evaluated in two multicenter, prospective, open-label clinical studies (one study in adults and adolescents ≥12 years of age and one pediatric study in children <12 years of age) in previously treated patients (PTPs) with severe hemophilia A (<5% endogenous Factor VIII activity or a documented genetic mutation consistent with severe hemophilia A). All studies evaluated the efficacy of routine prophylaxis with a weekly dose of 50 IU/kg and determined hemostatic efficacy in the treatment of bleeding episodes and during perioperative management in subjects undergoing major or minor surgical procedures. The completed adult and adolescent study enrolled a total of 159 PTPs (158 male and 1 female subjects) with severe hemophilia A. Subjects were aged 12 to 72 years and included 25 adolescent subjects aged 12 to 17 years. All 159 enrolled subjects received at least one dose of ALTVIIIO and were evaluable for efficacy. A total of 149 subjects (93.7%) completed the study. The ongoing pediatric study enrolled 67 male PTPs <12 years of age with severe hemophilia A (31 subjects were 1 to 5 years of age and 36 were 6 to 11 years of age) at data cut-off. Of the 67 enrolled subjects, all received at least 1 dose of ALTVIIIO.

Routine Prophylaxis to Reduce Bleeding Episodes

Adult and Adolescent Study

The efficacy of weekly 50 IU/kg ALTVIIIO as routine prophylaxis was evaluated as estimated by the mean annualized bleed rate (ABR) and by comparing the ABR during on-study prophylaxis vs. the ABR during pre-study FVIII prophylaxis. A total of 133 adults and adolescents, who were on pro-study FVIII prophylaxis, were assigned to receive ALTVIIIO for routine prophylaxis at a dose of 50 IU/kg IV once weekly for 26 weeks (Arm A). An additional 26 subjects, who were on pre-study episodic (on-demand) treatment with FVIII, received episodic (on-demand) treatment with ALTVIIIO at doses of 50 IU/kg IV for 26 weeks, followed by routine prophylaxis at a dose of 50 IU/kg IV once weekly for 26 weeks (Arm B). Overall, 159 subjects received at least a total number of 50 exposure days (EDs) in Arm A and 17 subjects completed at least 25 EDs of routine prophylaxis in Arm B. The ABR in subjects evaluable for efficacy with at least 26 weeks of exposure are summarized in Table 6. Routine prophylaxis resulted in a mean ABR (95% CI) of 0.7 (0.1, 1.0), a median (Q1; Q3) ABR of 0 (0, 0), and a median (Q1; Q3) ABR of 0 (0, 1.0), and a median (Q1; Q3) ABR of 0 (0, 1.0), and a median (Q1; Q3) ABR of 0 (0, 1.0), and a median (Q1; Q3) ABR of 0 (0, 1.0), and a median (Q1; Q3) ABR of 0 (0, 1.0), and a median (Q1; Q3) ABR of 0 (0, 1.0), and a median (Q1; Q3) ABR of 0 (0, 1.0), and a median (Q1; Q3) ABR of 0plasticity. The hemostatic response was rated as "excellent" in 13 of 13 surgeries (100%). No surgery had an outcome rated as "poor/none" or "missing.

Types of major surgeries assessed included major orthopedic procedures such as joint arthroplasties (joint replacements of knee, hip, and elbow), joint revisions and ankle fusion. Other major surgeries included molar extractions and rhinoplasty/mentoplasty.

Perioperative Management of Bleeding

Perioperative hemostasis was assessed in 13 major surgeries in 12 subjects (11 adults and 1 child). Of the 13 major surgeries, 12 surgeries required a single pre-operative dose to maintain hemostasis during surgery; for 1 major surgery during routine prophylaxis no pre-operative loading dose was administered on the day of/after before surgery. The median dose per pre-operative injection was 49.96 IU/kg (range 12.7 – 61.9).

The clinical evaluation of hemostatic response during major surgery was assessed using a 4-point scale of excellent, good, moderate, or poor/negative. The hemostatic effect of ALTVIIIO was rated as "excellent" in 13 of 13 surgeries (100%). No surgery had an outcome rated as "poor/none" or "missing." Types of major surgeries assessed included major orthopedic procedures such as joint arthroplasties (joint replacements of knee, hip, and elbow), joint revisions and ankle fusion. Other major surgeries included molar extractions and rhinoplasty/mentoplasty.

Perioperative hemostasis was assessed in 22 minor surgeries in 19 subjects (12 adults and 7 children). The hemostatic response was evaluated by the investigator/surgeon in 15 of these minor surgeries; an excellent response was reported in all (100%).

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

ALTVIIIO is supplied in kits comprising a single-dose vial containing nominally, 250, 500, 750, 1000, 2000, 3000, or 4000 international units (IU) of Factor VIII potency, a prefilled syringe with 3 mL sterile water for injection, and a sterile vial adapter (reconstitution device). The actual amount of ALTVIIIO in IU is stated on the label and carton of each vial. Not made with natural rubber latex.

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Arm A Prophylaxis</th>
<th>Arm B On-demand</th>
<th>Arm B Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean ABR (95% CI)</td>
<td>0.7 (0.1, 1.0)</td>
<td>0 (0, 0)</td>
<td>0 (0, 0)</td>
</tr>
<tr>
<td>Median ABR (Q1; Q3)</td>
<td>0 (0, 0)</td>
<td>0 (0, 0)</td>
<td>0 (0, 0)</td>
</tr>
<tr>
<td>subjects with zero bleeds, n (%)</td>
<td>82 (64.1)</td>
<td>0</td>
<td>20 (76.9)</td>
</tr>
</tbody>
</table>

Table 6: Summary of Annualized Bleeding Rate (ABR) with ALTVIIIO Prophylaxis, ALTVIIIO On-demand Treatment, and After Switch to ALTVIIIO Prophylaxis in Patients ≥12 Years of Age (continued)
ALTUVIIIO™ (al too’vee oh)

[antihemophilic factor (recombinant), Fc-VWF-XTN fusion protein-ethyl]

for intravenous use after reconstitution only

Single-dose vial

Please read this Patient Information carefully before using ALTUVIIIO and each time you get a refill, as there may be new information. This Patient Information does not take the place of talking with your healthcare provider about your medical condition or your treatment.

What is the most important information I need to know about ALTUVIIIO?

Do not attempt to give yourself an injection unless you have been taught how by your healthcare provider or hemophilia center.

You must carefully follow your healthcare provider’s instructions regarding the dose and schedule for injecting ALTUVIIIO so that your treatment will work best for you.

What is ALTUVIIIO?

ALTUVIIIO is an injectable medicine that is used to control and reduce the number of bleeding episodes in people with Hemophilia A (congenital Factor VIII deficiency).

Your healthcare provider may give you ALTUVIIIO when you have surgery.

Who should not use ALTUVIIIO?

You should not use ALTUVIIIO if you had an allergic reaction to it in the past.

What should I tell my healthcare provider before using ALTUVIIIO?

Talk to your healthcare provider about:

- Any medical problems that you have or had.
- All prescription and non-prescription medicines that you take, including over-the-counter medicines, supplements or herbal medicines.
- Pregnancy or if you are planning to become pregnant. It is not known if ALTUVIIIO may harm your unborn baby.
- Breastfeeding. It is not known if ALTUVIIIO passes into the milk and if it can harm your baby.

How should I use ALTUVIIIO?

You get ALTUVIIIO as an injection into your vein. Your healthcare provider will instruct you on how to do injections on your own, and may watch you give yourself the first dose of ALTUVIIIO.

Contact your healthcare provider right away if bleeding is not controlled after using ALTUVIIIO.

What are the possible side effects of ALTUVIIIO?

You can have an allergic reaction to ALTUVIIIO. Call your healthcare provider or emergency department right away if you have any of the following symptoms: difficulty breathing, chest tightness, swelling of the face, rash or hives.

Your body can also make antibodies called “inhibitors” against ALTUVIIIO. This can stop ALTUVIIIO from working properly. Your healthcare provider may give you blood tests to check for inhibitors. The common side effects of ALTUVIIIO are headache, joint pain, and back pain.

These are not the only possible side effects of ALTUVIIIO. Tell your healthcare provider about any side effect that bothers you or does not go away.

What are the ALTUVIIIO dosage strengths?

ALTUVIIIO comes in seven different dosage strengths with 3 mL sterile water for injection (swFI). The actual number of international units (IU) of Factor VIII activity in the vial will be imprinted on the label and on the box. The seven different strengths are as follows:

<table>
<thead>
<tr>
<th>Strength</th>
<th>Cap Color</th>
</tr>
</thead>
<tbody>
<tr>
<td>250 IU</td>
<td>Yellow</td>
</tr>
<tr>
<td>500 IU</td>
<td>Red</td>
</tr>
<tr>
<td>750 IU</td>
<td>Garnet</td>
</tr>
<tr>
<td>1000 IU</td>
<td>Green</td>
</tr>
<tr>
<td>2000 IU</td>
<td>Royal Blue</td>
</tr>
<tr>
<td>3000 IU</td>
<td>Mist Grey</td>
</tr>
<tr>
<td>4000 IU</td>
<td>Orange</td>
</tr>
</tbody>
</table>

Always check the actual dosage strength printed on the label to make sure you are using the strength prescribed by your healthcare provider.

How should I store ALTUVIIIO?

- Keep ALTUVIIIO in its original package.
- Protect it from light.
- Do not freeze.
- Store refrigerated 2°C to 8°C (36°F to 46°F) up to 48 months or at temperature [not to exceed 30°C (86°F)], for a single period up to 6 months. Do not use ALTUVIIIO after the expiration date printed on the label and carton of each vial.
- When storing at room temperature:
  - Note on the carton the date on which the product is removed from refrigeration.
  - Use the product before the end of this 6-month period or discard it.
  - Do not return the product to the refrigerator.

After mixing with the diluent:

- Do not use ALTUVIIIO if the mixed solution is not clear and colorless to slightly yellowish.
- Use mixed product as soon as possible.
- You may store mixed ALTUVIIIO at room temperature, not to exceed 30°C (86°F), for up to 3 hours. Protect the mixed ALTUVIIIO from direct sunlight. Discard any mixed ALTUVIIIO not used within 3 hours.

ALTUVIIIO™ is a trademark of Bioverativ Therapeutics Inc.

For patent information: https://www.sanofi.us/en/products-and-resources/patents
What else should I know about ALTUVIIIO?

Medicines are sometimes prescribed for purposes other than those listed here. Do not use ALTUVIIIO for a condition for which it was not prescribed. Do not share ALTUVIIIO with other people, even if they have the same symptoms that you have.

Manufactured by:
Bioverativ Therapeutics Inc.
Waltham, MA 02451
A SANOFI COMPANY
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ALTUVIIIO™ is a trademark of Bioverativ Therapeutics Inc.

INSTRUCTIONS FOR USE

ALTUVIIIO™ (al too’vee oh)
[antihemophilic factor (recombinant), Fc-VWF-XTEN fusion protein-ectH]
for intravenous use after reconstitution only
Single-dose vial

Read the Instructions for Use before you start using ALTUVIIIO and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or your treatment. Your healthcare provider should show you or your caregiver how to mix (reconstitute) and give ALTUVIIIO the first time ALTUVIIIO is used.

Any further questions? Ask your healthcare provider or call 1-800-633-1610.

Important Information You Need to Know Before Injecting ALTUVIIIO

It is important that you do not try to inject ALTUVIIIO unless you have received training from a healthcare provider.

- Read all of the instructions carefully before using the ALTUVIIIO.
- ALTUVIIIO is supplied as a single-dose vial of powder for mixing (reconstitution). Before you inject ALTUVIIIO, you must mix (reconstitute) ALTUVIIIO powder with liquid (diluent) that comes in a prefilled diluent syringe.
- After the powder and diluent are mixed the medicine is given in the vein (intravenous injection).
- The vial and the diluent syringe are not made with natural rubber latex.
- Do not use ALTUVIIIO if it has been dropped on a hard surface or damaged.
- Do not use if the syringe cap has been removed or is not securely attached.
- Do not use the mixed ALTUVIIIO if it contains visible particles or is cloudy.
- Do not give mixed ALTUVIIIO in the same tubing or container with other medicines.

Preparing to Inject ALTUVIIIO

Mixing (Reconstitution)

Step 1:
Look at the ALTUVIIIO kit:
- Check that you have the correct medicine and dose.
- Check the expiration date.
▲ Do not use ALTUVIIIO if the expiration date has passed.

Step 2:
Wash your hands with soap and water. Find a clean, flat work surface. Remove the supplies from the carton:
- Vial adapter in its package
- Vial with powdered medicine
- Plunger rod
- Prefilled diluent syringe
Also ensure you have the following supplies (not included in the carton):
- Infusion set
- Tourniquet
- 2 alcohol wipes
- 1 cotton ball or gauze pad
- 1 adhesive bandage, if required (See Step 22)
- 1 tape, if required (See Step 20)
- 1 larger luer lock syringe, if required (See Step 13)
- FDA-cleared sharps disposal container (See Step 23)
▲ Do not use ALTUVIIIO (vial or prefilled diluent syringe) if it has been dropped on a hard surface or damaged.
Step 3: Allow the ALTUVIIIO vial and the prefilled diluent syringe to come to room temperature before use. 
▲ Do not use external heat sources such as putting the vial or prefilled diluent syringe in hot water. 
▲ Do not put ALTUVIIIO in direct sunlight. 
▲ Do not return room temperature ALTUVIIIO to the refrigerator.

Step 4: Remove the plastic cap from the ALTUVIIIO vial. Wipe the rubber stopper of the vial with an alcohol wipe and allow it to dry. After cleaning, do not touch the rubber stopper with your hand or allow it to touch any surface.

Step 5: Completely remove the backing from the vial adapter package by peeling back the lid. Do not remove the vial adapter from the package or touch the inside of the vial adapter.

Step 6: Keep the vial on a flat surface. Hold the vial with one hand and using the other hand, place the vial adapter in its package over the vial. Note: The spike should be placed directly above the center of the rubber stopper. 
- Push the vial adapter straight down until the spike on the vial adapter punctures the center of the vial stopper and is fully inserted.

Step 7: Lift the package cover away from the vial adapter and throw away the cover.

Step 8: Note: Only use the prefilled diluent syringe provided to mix (reconstitute) the powdered medicine. 
- Hold the plunger rod by the circular disk. 
- Place the tip of the plunger rod into the end of the prefilled diluent syringe. 
- Turn the plunger rod to the right until it is firmly attached.

Step 9: With one hand, hold the prefilled diluent syringe directly under the cap with the cap pointing up. Note: Make sure you are holding the prefilled diluent syringe by the ridged part directly under the cap. 
▲ Do not use if the cap has been removed or is not securely attached.

Step 10: With your other hand, grasp the cap and bend it at a 90-degree angle until it snaps off. Note: After the cap snaps off, you will see the glass tip of the prefilled diluent syringe. 
▲ Do not touch the glass tip of the prefilled diluent syringe or the inside of the cap.

Step 11: Note: Be sure the vial is sitting on a flat surface. 
- Insert the tip of the prefilled diluent syringe into the vial adapter opening. 
- Turn the prefilled diluent syringe to the right until it is securely attached to the vial adapter.

Step 12: Slowly push down on the plunger rod to inject all of the liquid (diluent) from the prefilled diluent syringe into the vial. Note: The plunger rod may rise slightly afterward. This is normal.
**Step 13:**
With the prefilled diluent syringe still connected to the adapter, gently swirl the vial until the powder is completely dissolved. Check the solution through the vial to make sure the powder is fully dissolved.

*Note:* The solution should look clear and colorless to slightly yellowish. **Do not** shake.

**Do not** use the mixed (reconstituted) ALTUVIIIO if it contains visible particles or is cloudy.

**POOLING:** Pooling is the process of combining two or more reconstituted vials into a larger luer lock syringe (not provided in the carton). If the dose requires more than one vial, reconstitute each vial as described above (See Steps 4–13) with the prefilled diluent syringe provided. **Do not** detach the prefilled diluent syringe until you are ready to attach the large luer lock syringe to the next vial. Keep the vial adapter attached to the vial as you will need it for attaching a large luer lock syringe. Use a larger luer lock plastic syringe to combine the contents of the reconstituted vials into the syringe, similar as described in the Steps 14–15. Repeat this pooling procedure with each vial you will be using. Once you have pooled the required dose, proceed with Step 16 (Injecting ALTUVIIIO) using the larger luer lock syringe.

**Step 14:**
Make sure the plunger rod is pressed all the way down and the syringe is firmly attached to the vial adapter.

Turn the vial upside-down. Slowly pull down on the plunger rod to draw all the solution from the vial into the syringe.

*Note:* Be careful not to pull the plunger rod completely out of the syringe.

**Step 15:**
Gently unscrew the syringe from the vial adapter by turning it to the right. Throw away (dispose of) the vial with the adapter still attached (See Step 23).

If you are not ready to inject, put the syringe cap carefully back onto the syringe tip.

**Do not** touch the syringe tip or the inside of the cap.

*Note:* Mixed (reconstituted) ALTUVIIIO should be given within 3 hours after mixing. Protect from direct sunlight. Do not refrigerate after reconstitution.

**Step 16:**
Using aseptic technique (clean and germ free), attach the syringe to the connector end of the infusion set tubing by turning it to the right until securely attached.

**Do not** push ALTUVIIIO through the needle.

**Step 17:**
Apply a tourniquet to the upper arm. Then, using a new alcohol wipe, clean the skin where you will insert the needle and wait for it to dry.

**Step 18:**
Prime the syringe and the tubing. Push the plunger rod until all air is removed from the syringe and ALTUVIIIO has filled the infusion set needle.

**Do not** touch the needle and do not put the needle cover back onto needle after use.

- Insert the needle on the infusion set tubing into the vein as instructed by your healthcare provider.

**Step 20:**
Use tape to secure the plastic wings of the needle in place at the injection site if needed. Remove the tourniquet.

*Note:* Always make sure you have correctly inserted the needle into a vein when you perform an intravenous injection.

ALTUVIIIO is given in the vein (intravenous injection) after mixing (reconstitution) of the powdered medicine with the diluent. These are very generic instructions so your healthcare provider should teach you how to inject ALTUVIIIO. After you have been taught to self-inject, you can follow these instructions.

**Do not** give mixed (reconstituted) ALTUVIIIO if it contains particles, is discolored, or is cloudy.
Step 21:

Slowly push the plunger rod on the syringe all the way down to give ALTUVIIIO.
Your healthcare provider will provide your rate of administration based on your comfort level and the minimum injection time recommendation per vial.

Note: A small amount of medicine will be left in the infusion set after injection. This is normal.

Step 22:

After delivering ALTUVIIIO, remove the tape and the needle from the vein. Use a cotton ball or gauze pad to put pressure on the injection site for several minutes to stop any bleeding.

Note: You may apply an adhesive bandage if needed.

Step 23:

Put the infusion set and the syringe in FDA-cleared sharps disposal container right away after use.
Dispose of all unused solution according to your local regulations.
Dispose of all empty vial(s), and other used medical supplies in your household trash.

▲Do not throw away (dispose of) the infusion set or syringe in your household trash.

Disposing of ALTUVIIIO

Throw away (dispose of) the infusion set and the syringe in FDA-cleared sharps disposal container right away after use.
If you do not have FDA-cleared sharps disposal container you may use a household container that is:
– made of a heavy-duty plastic,
– can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out,
– upright and stable during use,
– leak-resistant, and
– properly labeled to warn of hazardous waste inside the container.

When your FDA-cleared sharps disposal container is almost full, you will need to follow your community guidelines for the right way to dispose of FDA-cleared sharps disposal container. There may be state or local laws about how you should throw away used ALTUVIIIO supplies.

▲Do not dispose of your used FDA-cleared sharps disposal container in your household trash unless your community guidelines permit this.

▲Do not recycle your used FDA-cleared sharps disposal container.
Keep your FDA-cleared sharps disposal container out of the reach of children.

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