PRODUCT MONOGRAPH

INCLUDING PATIENT MEDICATION INFORMATION

[Pr]**ALTUVIIIO®**

Antihemophilic Factor VIII (Recombinant, B-Domain deleted), Fc-VWF-XTEN fusion protein

Lyophilized powder

Intravenous

250, 500, 1000, 2000, 3000, or 4000 IU/vial

Antihemorrhagic Blood Coagulation Factor VIII

B02BD02

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Sections or subsections that are not applicable at the time of authorization are not listed.

PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

ALTUVIIIO® (Antihemophilic Factor VIII (Recombinant, B-Domain deleted), Fc-VWF-XTEN fusion protein) is indicated in adults, adolescents and children with hemophilia A (congenital Factor VIII [FVIII] deficiency) for:

- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes
- Treatment and control of bleeding episodes
- Perioperative management of bleeding (surgical prophylaxis)

ALTUVIIIO is not indicated for the treatment of von Willebrand's disease.

1.1 Pediatrics

Pediatrics (<18 years of age): Based on the data submitted and reviewed by Health Canada, the safety and efficacy of ALTUVIIIO in pediatric patients has been established. Therefore, Health Canada has authorized an indication for pediatric use (See 10.3 Pharmacokinetics).

1.2 Geriatrics

Geriatrics (>65 years of age): Clinical studies of ALTUVIIIO did not include sufficient number of patients 65 years of age and older to determine whether or not they respond differently from younger patients.

2 CONTRAINDICATIONS

ALTUVIIIO is contraindicated in patients who have had severe hypersensitivity reactions, including anaphylaxis, to the product or its components. For a complete listing see 6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING.

4 DOSAGE AND ADMINISTRATION

For intravenous use after reconstitution only.

4.1 Dosing Considerations

- Treatment with ALTUVIIIO should be initiated under the supervision of a qualified healthcare professional experienced in the treatment of hemophilia A.
- Each vial label of ALTUVIIIO states the FVIII potency in international units (IU). One IU corresponds to the activity of FVIII contained in one milliliter of normal human plasma.
- Potency assignment was determined in clinical studies using an activated partial thromboplastin time (aPTT)-based one-stage clotting assay with the Actin®-FSL reagent (see 10.3 Pharmacokinetics). It is recommended to use a validated one-stage clotting assay to measure FVIII activity.

- The FVIII activity level is higher (overestimated) when using chromogenic assay and a specific ellagic acid based aPTT reagent in one-stage clotting assay by approximately 2.5-fold. If these assays are used, this fold-increase should be accounted for to normalize FVIII activity levels. The ALTUVIIIO Factor VIII activity may also be underestimated by approximately 40% by a specific silica-based/synthetic phospholipid containing aPTT reagent in the one-stage clotting assay (see 7 WARNINGS AND PRECAUTIONS).

4.2 Recommended Dose and Dosage Escalation

For the dose of 50 IU/kg, the expected in vivo peak increase in FVIII level expressed as IU/dL (or % of normal) is estimated using the following formula:

Estimated Increment of FVIII (IU/dL or % of normal) = 50 IU/kg x 2 (IU/dL per IU/kg)

Routine Prophylaxis
The recommended dosing for routine prophylaxis for adults and children is 50 IU/kg of ALTUVIIIO administered once weekly.

Treatment and Control of Bleeding Episodes
ALTUVIIIO dosing for the treatment and control of bleeding episodes is provided in Table 1.

Table 1. Dosing for Treatment and Control of Bleeding Episodes

Type of Bleeding	Recommended dose	Additional information
Minor and Moderate For example: uncomplicated joint bleeds, minor muscular bleeds, mucosal or subcutaneous bleeds	Single dose of 50 IU/kg	For minor and moderate bleeding episodes occurring within 2 to 3 days after a prophylactic dose, a lower dose of 30 IU/kg dose may be used. Additional doses of 30 or 50 IU/kg every 2 to 3 days may be considered.
Major For example: Intracranial, retroperitoneal, iliopsoas and neck bleeds, muscle bleeds with compartment syndrome and bleeds associated with a significant decrease in the hemoglobin level	Single dose of 50 IU/kg	Additional doses of 30 or 50 IU/kg every 2 to 3 days may be considered.

When resuming prophylaxis 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. Thereafter, prophylaxis can be continued as usual on the patient's regular dosing schedule.

Perioperative Management

ALTUVIIIO dosing for perioperative management is provided in Table 2.

Table 2. Dosing for Perioperative Management

Type of Surgery	Pre-operative dose	Post-operative dose
Minor surgery	Single dose of 50 IU/kg	An additional dose of 30 or 50 IU/kg after 2 to 3 days may be considered.
Major surgery For example: Intracranial, intra-abdominal, joint replacement surgery, or complicated dental procedures	Single dose of 50 IU/kg	Additional doses of 30 or 50 IU/kg every 2 to 3 days may be administered as clinically needed for perioperative management.

4.3 Reconstitution

Table 3 - Reconstitution

Vial Size	Volume of Sterile Water for Injection to be Added to Vial	Approximate Available Volume	Concentration per mL
250 IU	3 mL	3 mL	83 IU
500 IU	3 mL	3 mL	167 IU
1000 IU	3 mL	3 mL	333 IU
2000 IU	3 mL	3 mL	667 IU
3000 IU	3 mL	3 mL	1000 IU
4000 IU	3 mL	3 mL	1333 IU

The reconstituted product can be stored at room temperature up to 30°C for 3 hours (see 11 STORAGE, STABILITY AND DISPOSAL).

4.4 Administration

For Intravenous Use Only After Reconstitution

ALTUVIIIO is administered by intravenous infusion after reconstitution of the drug powder with the diluent.

The entire dose of ALTUVIIIO should be injected intravenously slowly over 1 to 10 minutes, based on the patient's comfort level.

Do not administer reconstituted ALTUVIIIO if it contains particles, is discolored, or is cloudy.

Healthcare professionals should administer the first dose of ALTUVIIIO and monitor the patient for hypersensitivity reactions during the infusion and to establish the rate of infusion most appropriate for the patient. Subsequent doses may be given by the patient or the patient's caregiver only when they are properly trained in monitoring hypersensitivity reactions and the patient or caregiver are comfortable administering ALTUVIIIO outside of a healthcare setting.

Detailed instructions for preparation and administration are included in the Patient Medication Information section.

Dispose of all unused solution, empty vials, and used needles and syringes in an appropriate container and dispose of this container according to local requirements.

5 OVERDOSAGE

For management of a suspected drug overdose, contact your regional poison control centre.

6 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 4 – Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
Intravenous injection	Lyophilized powder for reconstitution Presentation 250, 500, 1000, 2000, 3000, and 4000 IU/vial.	arginine hydrochloride, calcium chloride dihydrate, histidine, polysorbate 80 and sucrose.

ALTUVIIIO is supplied in kits comprising:
- a single-use pack containing a powder vial (type 1 glass) with a chlorobutyl rubber stopper and an aluminum seal with a colored polypropylene flip-off cap at various strengths (see Table 4)
- a pre-filled syringe with 3 mL sterile water for injection (type 1 glass) with a bromobutyl rubber plunger stopper and tamper proof tip cap
- a sterile vial adapter reconstitution device.

7 WARNINGS AND PRECAUTIONS

Immune

Hypersensitivity Reactions

Allergic type hypersensitivity reactions, including anaphylaxis, are possible with FVIII replacement therapies, and may occur following treatment with ALTUVIIIO. Advise patients to discontinue use of ALTUVIIIO if hypersensitivity symptoms occur and to contact a physician and/or seek immediate emergency care.

Neutralizing Antibodies (Inhibitors)

Neutralizing FVIII antibodies have been reported in hemophilia A patients treated with FVIII replacement therapies. Monitor all patients for the development of FVIII inhibitors, by appropriate clinical observations and laboratory tests. If the patient's plasma FVIII level fails to increase 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 Monitoring and Laboratory results).

Monitoring Laboratory Tests

Routine monitoring of FVIII activity levels for prophylactic dose adjustment is not necessary based on experience from clinical studies. If assessment of plasma FVIII activity is needed, it is recommended to use a validated aPTT-based one-stage clotting assay (see 4.1 Dosing Considerations). The same assay, reagent, qualified laboratory, and equipment are recommended when it is considered necessary to monitor a patient's FVIII activity over time.

Monitor for the development of FVIII inhibitors. If bleeding is not controlled with ALTUVIIIO and the expected FVIII activity plasma levels are not attained, use a validated assay to determine if FVIII inhibitors are present (use Bethesda Units to titer inhibitors).

Reproductive Health: Female and Male Potential

- **Fertility**
  ALTUVIIIO has not been evaluated in animal fertility studies. It is not known whether ALTUVIIIO can affect fertility or sperm development in hemophilia A patients, although ALTUVIIIO is not expected to interact with DNA or be mutagenic (see Repeat Dose toxicity). No impact on male or female reproductive organs was shown in toxicology studies.

7.1 Special Populations

7.1.1 Pregnant Women

Animal reproductive studies have not been conducted with ALTUVIIIO. It is not known whether ALTUVIIIO can affect reproductive capacity or cause fetal harm when given to pregnant women.

7.1.2 Breast-feeding

Lactation studies have not been conducted with ALTUVIIIO. It is not known whether ALTUVIIIO is excreted into human milk.

7.1.3 Pediatrics

Pediatrics (0-<18 years):

Safety, efficacy, and pharmacokinetics of ALTUVIIIO have been evaluated in 99 previously treated patients (PTPs) < 18 years of age, who received at least one dose of ALTUVIIIO as part of routine prophylaxis, treatment of bleeding episodes, or perioperative management. Adolescents (12 to < 18 years of age) were enrolled in the Phase 3 study (XTEND-1), and children < 12 years of age were enrolled in the Phase 3 pediatric study (XTEND-Kids). Thirty-eight subjects (38.4%) were <6 years of age, 36 (36.4%) subjects were 6 to <12 years of age, and 25 subjects (25.2%) were adolescents. Data from the pediatric study (74 subjects) showed no dosing adjustment was required for children < 12 years of age compared to adolescents and adults (see 10.3 Pharmacokinetics).

7.1.4 Geriatrics

Geriatrics (>65 years of age):

Clinical studies of ALTUVIIIO did not include sufficient number of patients 65 years of age and older to determine whether or not they respond differently from younger patients.

7.1.5 Hepatic and Renal impairment

Specific studies in patients with renal or hepatic impairment have not been performed.

8 ADVERSE REACTIONS

8.1 Adverse Reaction Overview

Adverse events were monitored in 2 completed Phase 3 clinical studies in PTPs. Adverse drug reactions (ADRs) (summarized in Table 5) were reported in 79 (33.9%) of the 233 subjects treated with routine prophylaxis or on-demand therapy. The most common ADRs (>10%) in adults and adolescents were headache (20.1%) and arthralgia (16.4%). In children below 12 years, pyrexia (12.2%) was the most common ADR (>10%).

8.2 Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. The adverse reaction rates observed in the clinical trials, therefore, may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials may be useful in identifying and approximating rates of adverse drug reactions in real-world use.

The safety of ALTUVIIIO has been evaluated in 159 subjects from a completed Phase 3 study (XTEND-1) in previously treated patients (PTPs) 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. Of the 159 evaluated subjects, 134 (84.3%) were adults (18 years of age and older) and 25 (15.7%) were adolescents (12 to < 18 years of age). There were 154 (96.9%) subjects treated for at least 26 weeks and 98 (61.6%) subjects treated for at least 52 weeks. A total of 152 (95.6%) subjects achieved at least 25 exposure days and 115 (72.3%) subjects achieved at least 50 exposure days with a median of 53.0 (range 2-63) for both exposure days and injections per subject. Adverse events (AEs) were monitored for a total of 151.5 subject-years.

In the pediatric study (XTEND-Kids), the safety of ALTUVIIIO prophylaxis was evaluated in 74 male PTPs <12 years of age with severe hemophilia A who received at least one dose of ALTUVIIIO. Sixty-six (89.2%) subjects achieved at least 50 exposure days with a median of 53.0 (range 3-72).

Table 5: Adverse Drug Reactions reported for ALTUVIIIO

System Organ Class	Preferred Term	N=233*	
		Number of Subjects (%)	Frequency Category
Nervous system disorders	Headache	35 (15)	Very common
Musculoskeletal and connective tissue disorders	Arthralgia	31 (13)	Very common
	Pain in extremity	10 (4)	Common
	Back pain	9 (4)	Common
General disorders and administration site conditions	Pyrexia	10 (4)	Common
Gastrointestinal disorders	Vomiting	7 (3)	Common

* 233 subjects across two completed Phase 3 clinical studies

8.2.1 Clinical Trial Adverse Reactions – Pediatrics

The observed safety profile of ALTUVIIIO was found to be consistent across pediatric and adult patients.

8.3 Less Common Clinical Trial Adverse Reactions

Thromboembolic events occurred in 1% (3/261) of patients in the long-term safety extension study; these three subjects had pre-existing risk factors for thromboembolic events.

8.3.1 Less Common Clinical Trial Adverse Reactions – Pediatrics

Not Applicable

9 DRUG INTERACTIONS

9.4 Drug-Drug Interactions

There are no known drug interactions reported with ALTUVIIIO. No drug interactions studies have been performed.

9.5 Drug-Food Interactions

No drug-food interaction studies have been conducted with ALTUVIIIO. Interactions with foods have not been established.

9.6 Drug-Herb Interactions

No drug-herb interaction studies have been conducted with ALTUVIIIO. Interactions with herbal products have not been established.

9.7 Drug-Laboratory Test Interactions

No drug-laboratory test interaction studies have been conducted with ALTUVIIIO. Interactions with laboratory tests have not been established.

10 CLINICAL PHARMACOLOGY

10.1 Mechanism of Action

ALTUVIIIO (recombinant coagulation FVIII Fc-Von Willebrand Factor-XTEN Fusion Protein [FVIIIFc-VWF-XTEN]) is a recombinant fusion protein that temporarily replaces the missing coagulation FVIII needed for effective hemostasis and has demonstrated a 3- to 4-fold prolonged half-life relative to other standard and extended half-life FVIII molecules.

ALTUVIIIO is a FVIII protein that is designed to be independent of endogenous VWF in order to overcome the half-life limit imposed by FVIII-VWF interactions. The D'D3 domain of VWF is the region that interacts with FVIII. Appending the D'D3 domain of VWF to a rFVIII-Fc fusion protein provides protection and stability to FVIII and prevents FVIII interaction with endogenous VWF, thus overcoming the limitation on FVIII half-life imposed by VWF clearance.

The Fc region of human immunoglobulin G1 (IgG1) binds to the neonatal Fc receptor (FcRn). FcRn is part of a naturally occurring pathway that delays lysosomal degradation of immunoglobulins by recycling them back into circulation and thus prolonging the plasma half-life of the fusion protein.

ALTUVIIIO contains 2 XTEN polypeptides, which further increase its pharmacokinetics (PK). In ALTUVIIIO, the natural FVIII B domain (except 5 amino acids) is replaced with the first XTEN polypeptide, inserted in between FVIII N745 and E1649 amino acid residues; and the second XTEN polypeptide is inserted in between the D'D3 domain and Fc.

10.2 Pharmacodynamics

Hemophilia A is a bleeding disorder characterized by a deficiency of functional coagulation FVIII, which leads to a prolonged clotting time in the activated partial thromboplastin time (aPTT)-based one-stage

clotting assay. Administration of ALTUVIIIO increases plasma levels of FVIII, temporarily correcting the coagulation defect in hemophilia A patients.

Based on FVIII exposure-response analyses, in a typical patient receiving an ALTUVIIIO 50 IU/kg once-weekly regimen, the probability of zero bleeds in 1 year was predicted to be 71% (95% CI: 50%-83%).

10.3 Pharmacokinetics

The pharmacokinetics (PK) of ALTUVIIIO were evaluated in 159 adults and adolescents and 74 children <12 years old, respectively, receiving weekly IV injections of 50 IU/kg. Among children <12 years old, 36 subjects had ALTUVIIIO single-dose PK profiles available.

PK parameters following a single dose of ALTUVIIIO are presented in Table 6. The PK parameters were based on plasma FVIII activity measured by the aPTT-based one-stage clotting assay using the Actin® FSL reagent. After a single dose of 50 IU/kg, ALTUVIIIO exhibited high sustained FVIII activity with prolonged half-life across age cohorts. There was a trend of decreasing AUC, and increasing clearance, with decreasing age in the pediatric cohorts. The PK profile at steady state (Week 26) was comparable with the PK profile obtained after the first dose.

Table 6: Pharmacokinetic parameters following a single dose of ALTUVIIIO by age (one-stage clotting assay with the Actin® FSL reagent)

PK parameters (mean SD)	Pediatric Study		Adult and Adolescent Study	
	1 to < 6 Years N=18	6 to < 12 Years N=18	12 to < 18 years N=25	Adults N=134
AUC (IU*h/dL)	6800 (1120)[b]	7190 (1450)	8350 (1550)	9850 (2010)[a]
$t_{1/2}$ (h)	38.0 (3.72)	42.4 (3.70)	44.6 (4.99)	48.2 (9.31)
CL (mL/h/kg)	0.74 (0.12)	0.68 (0.14)	0.58 (0.12)	0.49 (0.12)[a]
V_{ss} (mL/kg)	36.6 (5.59)	38.1 (6.80)	34.9 (7.38)	31.0 (7.32)[a]
MRT (hr)	49.6 (5.45)	56.3 (5.10)	60.0 (5.54)	63.9 (10.2)[a]

$AUC_{0\text{-}tau}$ = area under the activity-time curve over the dosing interval, CL = clearance, MRT = mean residence time, SD = standard deviation, $t_{1/2z}$ = terminal half-life, V_{ss} = volume of distribution at steady state
[a]Calculation based on 128 profiles. [b] N=17

In XTEND-1, ALTUVIIIO at steady state maintained normal to near normal (>40 IU/dL) FVIII activity for a mean (SD) of 4.1 (0.7) days with once-weekly prophylaxis in adults. The FVIII activity over 10 IU/dL was maintained in 83.5% of adults and adolescents throughout the study. In children <12 years, ALTUVIIIO maintained normal to near normal (>40 IU/dL) FVIII activity for 2 to 3 days and >10 IU/dL FVIII activity for approximately 7 days (see Table 7).

Table 7: Pharmacokinetic parameters at steady-state of ALTUVIIIO by age (one-stage clotting assay with the Actin® FSL reagent)

PK parameters Mean (SD)	Pediatric study		Adult and Adolescent study	
	1 to <6 years	6 to <12 years	12 to <18 years	Adults
	N=37	N=36	N=24	N=125
Peak (IU/dL)	136 (48.9)[a] (N=35)	131 (36.1) (N=35)	124 (31.2)	150 (35.0) (N=124)
IR (kg*IU/dL/IU)	2.22 (0.83)[b] (N=35)	2.10 (0.73) (N=35)	2.25 (0.61) (N=22)	2.64 (0.61)[c] (N=120)
Time to 40 IU/dL (h)	68.0 (10.5)[b]	80.6 (12.3)[b]	81.5 (12.1)[c]	98.1 (20.1)[c]
Time to 20 IU/dL (h)	109 (14.0)[b]	127 (14.5)[b]	130 (15.7)[c]	150 (27.7)[c]
Time to 10 IU/dL (h)	150 (18.2)[b]	173 (17.1)[b]	179 (20.2)[c]	201 (35.7)[c]
Trough (IU/dL)	10.9 (19.7) (N=36)	16.5 (23.7)	9.23 (4.77) (N=22)	18.0 (16.6)[d] (N=123)

Peak = 15 min post dose at steady state, IR = incremental recovery, Trough = predose FVIII activity value at steady state, SD = standard deviation

[a] Steady state peak, trough and IR were computed using available measurements at week 52/End of study PK sampling visit

[b] Time to FVIII activity was predicted using population PK model for pediatric study

[c] Time to FVIII activity was predicted using population PK model for adult study

11 STORAGE, STABILITY AND DISPOSAL

Storage Conditions

Unopened vials should be stored under controlled refrigeration (2°C - 8°C). The product may be stored at room temperature (up to 30°C) for a single 6-month period. The date that the product is removed from refrigeration should be noted on the carton.

Do not use beyond the expiration date printed on the carton and the vial or six months after removing the carton from refrigeration, whichever is earlier.

Do not freeze. Protect from light.

In use shelf-life

The reconstituted product can be stored at room temperature (up to 30°C) for 3 hours. Protect product from direct sunlight. After reconstitution, if the product is not used within 3 hours, it must be discarded.

The appearance of the reconstituted product should be clear and colorless to slightly opalescent.

Do not use this medicine if you notice that it is cloudy or contains visible particles.

PART II: SCIENTIFIC INFORMATION

13 PHARMACEUTICAL INFORMATION

Drug Substance

Proper name: Antihemophilic Factor VIII (Recombinant, B-Domain deleted), Fc-VWF-XTEN fusion protein

Chemical name: Recombinant coagulation factor VIII Fc - von Willebrand factor - XTEN fusion protein (rFVIIIFc-VWF-XTEN)

Molecular formula and molecular mass:
ALTUVIIIO is a fully recombinant fusion protein comprising a single chain B-domain deleted (BDD) analogue of human Factor VIII (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 2 XTEN polypeptides. It has a molecular weight of approximately 312 kDa.

Physicochemical properties: Antihemophilic Factor VIII (Recombinant, B-Domain deleted), Fc-VWF-XTEN fusion protein drug substance is a clear to slightly opalescent, colorless to slightly yellow solution, with pH of 6.5 to 7.2.

Product Characteristics:
Antihemophilic Factor VIII (Recombinant, B-Domain deleted), Fc-VWF-XTEN fusion protein is produced by recombinant DNA technology in a human embryonic kidney (HEK) cell line, which has been extensively characterized. Efanesoctocog alfa is manufactured without addition of human- or animal-derived components and purified by a combination of multiple chromatography steps, a detergent viral inactivation step, a nano filtration step for viral clearance, and ultrafiltration steps.

14 CLINICAL TRIALS

14.1 Clinical Trials by Indication

Routine Prophylaxis in Adults and Adolescents with Hemophilia A (congenital FVIII deficiency)

Study Design and Demographics

The safety and efficacy of ALTUVIIIO in adult and adolescent hemophilia A subjects (≥ 12 years of age) were evaluated in a Phase 3 multicenter open-label clinical study (XTEND-1), which enrolled a total of 159 PTPs (158 male and 1 female subjects) with severe disease (< 1% endogenous FVIII activity or a documented genetic mutation consistent with severe hemophilia A). Subjects were aged 12 to 72 years and included 25 adolescents aged 12 to 17 years.

Subjects enrolled on study were required to have platelet counts ≥ 100 x 10^9 cells/L and controlled HIV (CD4 lymphocyte count > 200 x10^6 cells/L and a viral load of < 400 copies/mL within 26 weeks of screening). Subjects were excluded if they had emicizumab treatment within 20 weeks of screening, serious infections, abnormal renal function (serum creatinine > 177 micromoles/L, abnormal, abnormal liver function (serum total bilirubin >3 x upper limit of normal [ULN] or investigator decision), any vaccination within 30 days of screening, a major surgery within 8 weeks of screening, and if they had a positive test for factor VIII inhibitor (≥0.6 Bethesda units [BU] per milliliter) at screening or a history of a positive inhibitor test, clinical signs or symptoms of a decreased response to factor VIII, other known coagulation disorders, a history of hypersensitivity or anaphylaxis to factor VIII therapies. A total of 149 subjects (93.7%) completed the study.

The study included 2 arms and in arm A, subjects received once-weekly prophylaxis with ALTUVIIIO (50 IU/Kg) intravenously for 52 weeks. In arm B, subjects received on-demand treatment with ALTUVIIIO (50 IU/Kg) intravenously for 26 weeks, followed by once-weekly prophylaxis with ALTUVIIIO (50 IU/Kg) intravenously for 26 weeks.

The primary end point was the mean annualized bleeding rate for treated bleeds in arm A and the key secondary end point was intrapatient comparison of the annualized bleeding rate (ABR) during prophylaxis in arm A with the ABR during pre-study factor VIII prophylaxis for subjects in Arm A who participated in a prospective observational study.

Table 8 – XTEND-1 Study Design to Assess the Safety and Efficacy of ALTVUVIIIO in Adults and Adolescents with Hemophilia A (congenital FVIII deficiency)

Study #	Study design	Dosage, route of administration and duration	Study subjects (n)	Age (years)	Sex
XTEND-1 (EFC16293)	Phase 3, open label, multi-center study in previously treated adult and adolescent with severe hemophilia A 2 arm study.	Arm A: once-weekly prophylaxis with ALTUVIIIO 50 IU/Kg intravenous injections for 52 weeks Arm B: on-demand treatment with ALTUVIIIO 50 IU/Kg intravenous injections for 26 weeks, followed by once-weekly prophylactic doses of 50 IU/Kg intravenous ALTUVIIIO injections for 26 weeks	159	12-72	M: 158 F: 1

Study Results

A total of 133 adults and adolescents, who were on pre-study FVIII prophylaxis, were assigned to receive ALTUVIIIO for routine prophylaxis at a dose of 50 IU/kg IV once weekly for 52 weeks (Arm A). Of the 133 subjects, 128 subjects had at least 26 weeks of exposure to ALTUVIIIO and are included in the efficacy evaluation set. An additional 26 subjects, who were on pre-study episodic (on-demand) treatment with FVIII, received episodic (on-demand) treatment with ALTUVIIIO 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, 115 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. A total of 149 subjects (93.7%) completed the study.

The ABR in subjects evaluable for efficacy are summarized in Table 9. Routine prophylaxis resulted in a mean ABR (95% CI) of 0.7 (0.5, 1.0), a median (Q1, Q3) ABR of 0 (0, 1.0), and a median (Q1, Q3) annualized joint bleeding rate of 0 (0, 1.0). Eighty-two of 128 (64.1%) subjects experienced no bleeding episodes, and 92 of 128 (71.9%) of subjects experienced no joint bleeding episodes while on routine prophylaxis for a median of 52 weeks in Arm A.

Table 9: Summary of Annualized Bleeding Rate (ABR) with ALTUVIIIO prophylaxis, ALTUVIIIO on-demand treatment, and after switch to ALTUVIIIO prophylaxis in subjects ≥ 12 Years of Age

Endpoint[1]	Arm A Prophylaxis[2]	Arm B On demand[3]	Arm B Prophylaxis[3]
	N=128	N=26	N=26
Treated Bleeds			
Mean ABR (95% CI)[4]	0.7 (0.5, 1.0)	21.4 (18.8, 24.4)	0.7 (0.3, 1.5)
Median ABR (Q1, Q3)	0 (0, 1.0)	21.1 (15.1, 27.1)	0 (0, 0)
Subjects with zero bleeds, n (%)	82 (64.1)	0	20 (76.9)
Spontaneous bleeds			
Mean ABR (95% CI)[4]	0.3 (0.2, 0.4)	15.8 (12.3, 20.4)	0.4 (0.2, 1.2)
Median ABR (Q1, Q3)	0 (0, 0)	16.7 (8.6, 23.8)	0 (0, 0)
Subjects with zero bleeds, n (%)	103 (80.5)	1 (3.8)	22 (84.6)
Joint bleeds			
Mean ABR (95% CI)[4]	0.5 (0.4, 0.7)	17.5 (14.9, 20.5)	0.6 (0.3, 1.5)
Median ABR (Q1, Q3)	0 (0, 1.0)	18.4 (10.8, 23.9)	0 (0, 0)
Subjects with zero bleeds, n (%)	92 (71.9)	0	21 (80.8)

ABR = annualized bleed rate; CI = confidence interval; Q1 = 25th percentile; Q3 = 75th percentile.
[1] All analyses of bleeding endpoints are based on treated bleeds
[2]Subjects assigned to receive ALTUVIIIO prophylaxis for 52 weeks
[3]Subjects assigned to receive ALTUVIIIO for 26 weeks
[4]Based on negative binomial model

An intra-subject comparison of ABRs during on-study and pre-study prophylaxis yielded a reduction of 77% in ABR based on treated bleeds (95% CI: 58%, 87%) during routine prophylaxis with ALTUVIIIO compared to pre-study FVIII prophylaxis (see Table 10).

Table 10: Intra-Subject Comparison of Annualized Bleeding Rate (ABR) with ALTUVIIIO Prophylaxis versus Pre-study FVIII Prophylaxis in Subjects ≥ 12 Years of Age

Endpoint	On-study prophylaxis with ALTUVIIIO 50 IU/kg QW (N = 78)	Pre-study standard of care FVIII Prophylaxis[2] (N = 78)
Median Observation Period (weeks) (Q1, Q3)	50.1 (49.1, 51.2)	50.2 (43.9, 52.1)
Bleeds		
Mean ABR (95% CI)[1]	0.7 (0.4,1.1)	3.0 (2.0, 4.4)
Rate Ratio (95% CI)	0.23 (0.13, 0.42)	
Subjects with zero bleeds, n (%)	50 (64.1)	33 (42.3)
Median ABR (Q1, Q3)	0 (0, 1.0)	1.1 (0, 3.7)

ABR = annualized bleed rate based on treated bleeds; CI = confidence interval; Q1 = 25th percentile; Q3 = 75th percentile.

[1]Based on negative binomial model
[2]Prospective observational study (OBS16221)

Routine Prophylaxis in Children with Hemophilia A (congenital FVIII deficiency)

Study Design and Demographics

The safety and efficacy of ALTUVIIIO as routine prophylaxis in hemophilia PTPs <12 years of age was evaluated as estimated by the mean ABR. A total of 74 subjects with severe hemophilia A (38 subjects <6 years of age and 36 subjects 6 to <12 years of age) were enrolled to receive ALTUVIIIO for routine prophylaxis at a dose of 50 IU/kg IV once weekly for 52 weeks. Key inclusion and exclusion criteria were consistent with the pivotal Phase III study in adults and adolescents (XTEND-1).

The primary end point was the occurrence of inhibitor development in children <12 years of age. The key secondary end points reported are the ABR for treated bleeds, including a breakdown by spontaneous and joint bleeds, as well as the ABR based on all bleeding episodes (Table 11).

Table 11: Summary of Annualized Bleeding Rate (ABR) with ALTUVIIIO Prophylaxis in Patients <12 Years of Age

Endpoint*	**<6 years**	**6 to < 12 years**	**Overall**
	N = 38	N = 35†	N = 73†
Treated bleeds			
Mean ABR (95% CI)‡	0.5 (0.3, 0.8)	0.8 (0.4, 1.4)	0.6 (0.4, 0.9)
Median ABR (Q1, Q3)	0 (0, 1.0)	0 (0, 1.1)	0 (0, 1.0)
% subjects with zero bleeds, n (%)	24 (63.2)	23 (65.7)	47 (64.4)
Treated spontaneous bleeds			
Mean ABR (95% CI) ‡	0.2 (0.1, 0.4)	0.2 (0, 0.6)	0.2 (0, 0.3)
Median ABR (Q1, Q3)	0 (0, 0)	0 (0, 0)	0 (0, 0)
% subjects with zero bleeds, n (%)	32 (84.2)	32 (91.4)	64 (87.7)
Treated joint bleeds			
Mean ABR (95% CI) ‡	0.2 (0.1, 0.6)	0.4 (0.2, 0.9)	0.3 (0.2, 0.6)
Median ABR (Q1, Q3)	0 (0, 0)	0 (0, 0)	0 (0, 0)
% subjects with zero bleeds, n (%)	34 (89.5)	27 (77.1)	61 (83.6)
All bleeds (treated and untreated)*			
Mean ABR (95% CI) ‡	2.8 (1.4, 5.6)	2.3 (1.3, 4.1)	2.6 (1.6, 4.0)
Median ABR (Q1, Q3)	0 (0, 2.0)	1.0 (0, 2.9)	0 (0, 2.0)
% subjects with zero bleeds, n (%)	21 (55.3)	16 (45.7)	37 (50.7)

ABR = annualized bleed rate; CI = confidence interval; Q1= 25th percentile, Q3=75th percentile.

* Reflects all bleeds reported by patients including those where no ALTUVIIIO was administered.

† A subject in the 6 to <12 years old age group who received an intense consolidation treatment (2 to 3 injections per week for 15 weeks) after treatment of 2 traumatic hip joint bleeds was excluded from the efficacy analysis as the subject did not receive the weekly prophylaxis treatment as specified in the protocol for an extended period.

‡ Based on negative binomial model.

Perioperative Management of Bleeding (Surgical Prophylaxis)

Major surgeries

Perioperative hemostasis was assessed in 14 major surgeries in 13 subjects (11 adults and 2 pediatrics) across the two Phase 3 studies. Of the 14 major surgeries, 13 surgeries required a single pre-operative dose to maintain hemostasis during surgery; for 1 major surgery occurring during routine prophylaxis, no pre-operative loading dose was administered on the day of/or on the day before surgery. The clinical evaluation of hemostatic response during major surgery was assessed using a 4-point scale of excellent, good, moderate, or poor/none. The hemostatic effect of ALTUVIIIO was rated as "excellent" in 14 of 14 surgeries (100%).

Minor surgeries

Perioperative hemostasis was assessed in 32 minor surgeries in 28 subjects (15 adults and 13 adolescents and children) across the Phase 3 studies. The hemostatic response was evaluated by the investigator/surgeon in 25 of these minor surgeries; an excellent response was reported in all (100%).

14.3 Immunogenicity

All subjects were monitored for neutralizing antibodies (inhibitors) to FVIII during the ALTUVIIIO Phase 3 clinical studies. No subjects developed neutralizing antibodies to FVIII, consistent with results expected for PTPs switching to a new treatment.

The detection of antibodies that are reactive to FVIII is highly dependent on many factors, including the patient population studied (PTPs vs previously untreated patients [PUPs]), sensitivity and specificity of the assay, sample handling, timing of sample collection, concomitant medications, and underlying disease. Therefore, it may be misleading to compare the incidence of antibodies to ALTUVIIIO with the incidence of antibodies to other FVIII products. Since PUPs have not been enrolled in clinical studies, it is not yet possible to estimate inhibitor development to ALTUVIIIO.

During the ALTUVIIIO phase 3 studies (median treatment duration 96.3 weeks), 4/276 (1.4%) of evaluable patients developed transient treatment-emergent anti-drug antibodies (ADAs).

16 NON-CLINICAL TOXICOLOGY

General Toxicology

Single dose toxicity

No single-dose toxicology studies were performed with ALTUVIIIO.

Repeat Dose toxicity

A repeat-dose IV toxicity study in healthy monkeys administered up to 750 IU/kg/dose ALTUVIIIO every 4 days for 4 weeks showed increased activated partial thromboplastin time (aPTT). This is consistent with development of neutralizing antibodies against Antihemophilic Factor VIII (Recombinant, B-

Domain deleted), Fc-VWF-XTEN fusion protein, which cross-reacted to endogenous FVIII, as indicated by the prolonged aPTT and decreased endogenous FVIII activity. ADA-induced acquired hemophilia resulted in the death of one monkey on Day 30 due to excessive bleeding following blood sample collection. Greater group mean aPTT values persisted in females given 750 IU/kg/dose after the recovery period. There were no other adverse findings directly attributed to the pharmacologic activity/intended mechanism of ALTUVIIIO.

No specific nonclinical immunogenicity studies have been conducted with ALTUVIIIO. However, dose-related increases in ADA to Antihemophilic Factor VIII (Recombinant, B-Domain deleted), Fc-VWF-XTEN fusion protein were observed in rats and monkeys dosed every 3 or 4 days, respectively, for 4 weeks at doses up to 750 IU/kg/dose. Due to the formation of antibodies, which resulted in limited exposure in rats and monkeys by Day 28 or Day 29, respectively, it was not feasible to conduct meaningful toxicology studies beyond 4 weeks of dosing.

Carcinogenicity

No animal studies investigating carcinogenic effects of ALTUVIIIO have been conducted since it is a replacement protein factor for coagulation activity.

Genotoxicity

ALTUVIIIO has not been evaluated in mutagenicity or chromosomal aberration assays since it is a replacement protein factor for coagulation activity.

Reproductive and Developmental Toxicology

ALTUVIIIO has not been evaluated in animal reproduction studies. It is not known whether ALTUVIIIO can affect fertility or sperm development in hemophilia A patients. No adverse effects on male or female reproductive organs were observed in toxicology studies. Based on a well understood mechanism of action, FVIII replacement products are not expected to affect embryo-fetal development. Therefore, the developmental risk in humans is considered low for ALTUVIIIO.

Local tolerance

Local tolerance studies have not been conducted with ALTUVIIIO. However, ALTUVIIIO was well tolerated in 4-week repeat-dose IV toxicity studies in rats and monkeys.

Hemocompatibility

ALTUVIIIO showed no potential for hemolysis and no flocculation in an in vitro hemocompatibility study with human whole blood at concentrations up to 4.1 mcg/mL.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

[Pr]ALTUVIIIO

Antihemophilic Factor VIII (Recombinant, B-Domain deleted), Fc-VWF-XTEN fusion protein

Read this carefully before you start taking ALTUVIIIO and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about ALTUVIIIO.

What is ALTUVIIIO used for?

ALTUVIIIO is an injectable medicine that is used to help control and prevent bleeding in people with hemophilia A (congenital factor VIII deficiency).

How does ALTUVIIIO work?

- People with hemophilia A do not have enough natural coagulation factor VIII in their blood.
- Factor VIII is a protein produced naturally in the body. It helps the blood to form clots to stop bleeding.
- When your body does not produce enough coagulation factor VIII and you become injured, your blood will not form clots and you may bleed into and damage your muscles and joints.
- ALTUVIIIO is coagulation FVIII made using recombinant technology in a laboratory, which can be given by injection to help control and prevent bleeding in people with hemophilia A.
- ALTUVIIIO is a factor VIII fusion protein that raises the levels of Factor VIII to help prevent and/or control your bleeding and keeps levels high enough in most instances to require only a once a week injection.

What are the ingredients in ALTUVIIIO?

Medicinal ingredients: Antihemophilic Factor VIII (Recombinant, B-Domain deleted), Fc-VWF-XTEN fusion protein

Non-medicinal ingredients: Arginine hydrochloride, calcium chloride dihydrate, histidine, polysorbate 80 and sucrose

ALTUVIIIO comes in the following dosage forms:

ALTUVIIIO comes as a powder in a vial. It must be dissolved with the solvent (sterile water) supplied in the pre-filled syringe before use. ALTUVIIIO is available in 250, 500, 1000, 2000, 3000, and 4000 IU/vial.

Do not use ALTUVIIIO if:

- You are allergic to this drug, or any ingredient listed above (non-medicinal ingredients).
- The expiry date (printed on the vial) has passed. If you take this medicine after the expiry date has passed, it may not work well.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take ALTUVIIIO. Talk about any health conditions or problems you may have including the one's mentioned below:

Allergic Reactions

Allergic reactions, including severe events, are possible. Stop taking ALTUVIIIO if allergy symptoms occur and contact your doctor and/or seek immediate help.

Blood tests

Your doctor will monitor you to make sure ALTUVIIIO is working well. If your blood levels of FVIII decrease or if bleeding is not controlled after you are given ALTUVIIIO, this may indicate the presence of an inhibitor (neutralizing antibodies), and you may require a new treatment.

Other medicines and products

Tell your doctor, nurse or pharmacist if you are using, have recently used, or might use any other medicines.

Pregnancy and/or breastfeeding

- Talk to your doctor before using ALTUVIIIO if you are pregnant or breastfeeding, think you may be pregnant, or are planning to have a baby.
- There is no experience with the use of ALTUVIIIO in pregnant women.
- It is not known whether ALTUVIIIO passes into human breast milk. Tell your doctor if you are breast-feeding or plan to do so.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

How to take ALTUVIIIO:

Medical supervision is recommended the first time ALTUVIIIO is given, where proper medical care for severe allergic reactions can be provided. You or your caregiver should only take or give ALTUVIIIO after proper training and only when you feel comfortable to do so.

Usual dose:

Your doctor will tell you or your caregiver how much ALTUVIIIO to take or give and how often (usually once a week). You or your caregiver should always follow the specific instructions given by your healthcare professional.

Overdose:

Tell your doctor immediately.

If you think you, or a person you are caring for, have taken too much ALTUVIIIO contact a healthcare professional, hospital emergency department, or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

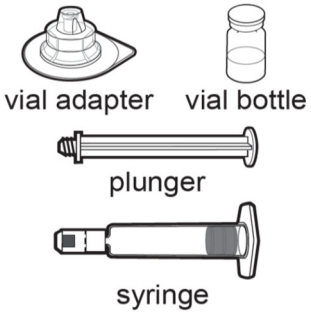
Talk to your doctor if you miss a dose.

Preparing your dose for administration:

These steps are general guidelines for using ALTUVIIIO. If you are unsure of these steps, please call your healthcare professional before taking or giving this drug.

RECONSTITUTION

Step 1:
Look at the product kit:
- Check that you have the correct product and dose with the right colour cap.
- Check the expiration date.
- Do not use the product if the expiration date has passed.

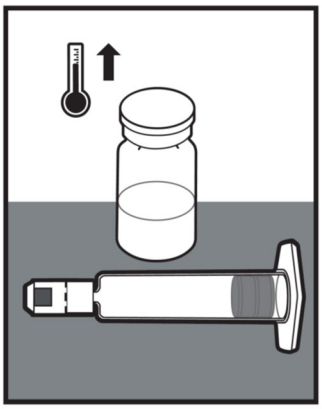


Find a clean, flat work surface. Remove the components from the carton: Vial adapter in its package, Vial with powdered drug, Plunger rod and Prefilled solvent syringe.

Also ensure you have the following supplies (not included in the carton): Infusion set (needle with plastic line), Tourniquet (large elastic band), 2 alcohol wipes, 1 cotton ball or gauze pad, 1 adhesive bandage, 1 tape, 1 larger luer lock syringe (if required; See Step 13) and a puncture-resistant container (See Step 23).

Do not use the product (vial and/or syringe) if it has been dropped on a hard surface or is damaged.

Step 2:

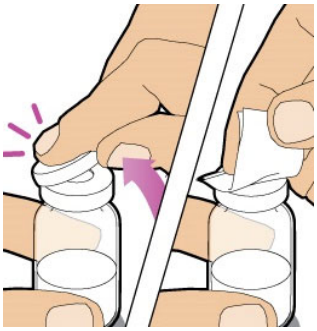


Allow the ALTUVIIIO vial and the syringe with solvent to come to room temperature.
Do not heat the vial or syringe with solvent using hot water or other means.
Do not put the product into direct sunlight.
Do not return the product to the refrigerator.

Step 3:

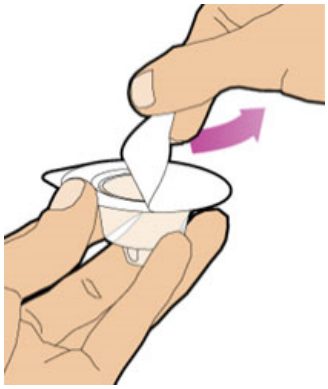
Wash your hands with soap and water.

Step 4:



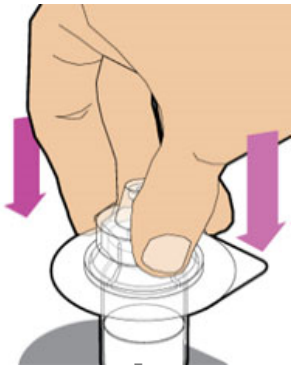
Remove the plastic cap from the ALTUVIIIO vial. Wipe the rubber stopper of the vial with an alcohol wipe and allow it to dry. After cleaning, **do not** touch the rubber stopper with your hand or allow it to touch any surface.

Step 5:



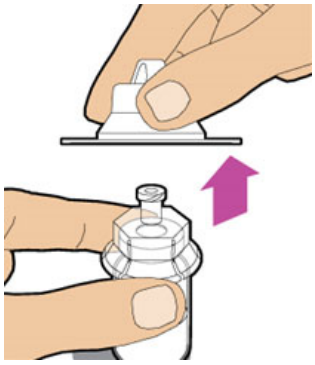
Completely remove the backing from the vial adapter package by peeling back the lid. **Do not** remove the vial adapter from the package or touch the inside of the vial adapter.

Step 6:



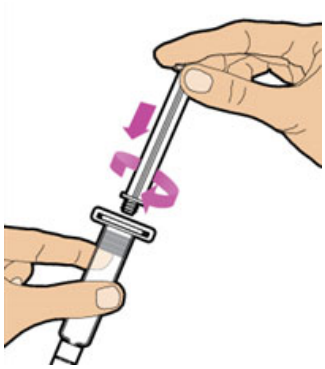
Keep the vial on a flat surface. Hold the vial with one hand and using the other hand, place the vial adapter in its package over the vial.
Note: The spike should be placed directly above the center of the rubber stopper.
Push the vial adapter straight down until the adapter spike punctures the center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

Step 7:



Lift the package cover away from the vial adapter and discard the cover and keep on a flat surface until Step 11.

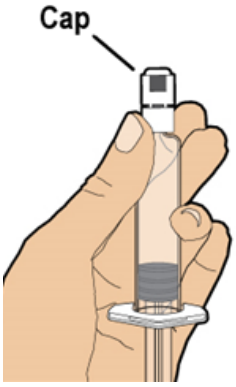
Step 8:



Note: Only use the syringe with solvent provided to dissolve the drug product.

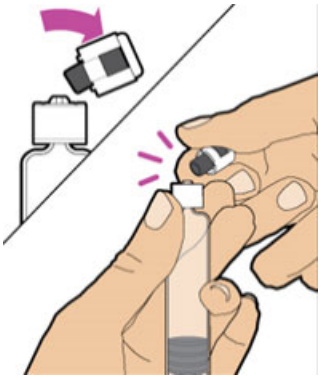
Hold the plunger rod at the circular disk (top hand in picture). Place the tip of the plunger rod into the end of the syringe. Turn the plunger rod in a clockwise (left to right) motion until it is firmly attached.

Step 9:



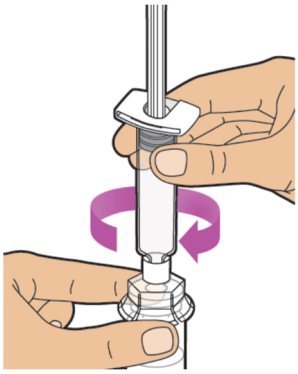
With one hand, hold the syringe with solvent right under the cap, and with the cap pointing up.
Note: Make sure you are holding the syringe by the ridged part directly under the cap.
Do not use if the cap has been removed or is not securely attached.

Step 10:



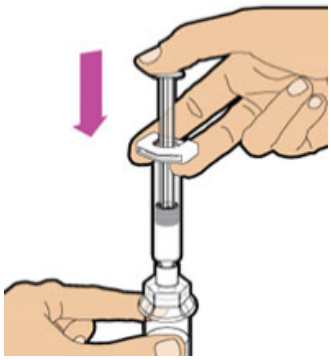
With your other hand, grasp the cap and bend it at a ninety-degree (90°) angle until it snaps off.
Note: After the cap snaps off, you will see the glass tip of the syringe.
Do not touch the glass tip of the syringe or the inside of the cap.

Step 11:



Note: Be sure the vial is sitting on a flat surface.
Turn the syringe over and insert the tip of the syringe into the vial adapter opening.
Turn the syringe in a clockwise (left to right) motion until it is securely attached to the vial adapter.

Step 12:



Slowly push the plunger rod down to inject all of the solvent from the syringe into the vial.
Note: The plunger rod may rise slightly afterward. This is normal.

Step 13:

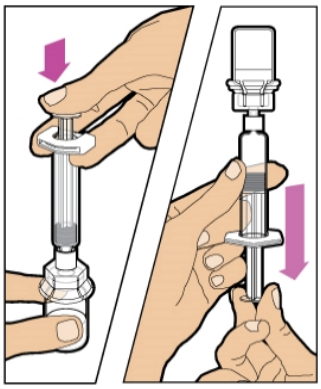
With the syringe still connected to the adapter, gently swirl the vial until the product is completely dissolved. Check the solution through the vial to make sure the powder is fully dissolved.

Note: The appearance of the solution should look clear and colourless. Your doctor will show you how the drug should look.

Do not shake. **Do not** use the ALTUVIIIO in solution if it contains visible particles or is cloudy. Check the solution through the vial to make sure the powder is fully dissolved.

POOLING: This is the process of combining two or more vials with the drug already in solvent into a larger syringe (not included in the carton and not pictured). If the dose requires more than one vial, combine each vial as described above (See Steps 4 – 13) with the syringe provided. **Keep** the syringe attached until you are ready to add the larger luer lock syringe to the next vial. 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 the Step 16 (administration) using the larger syringe. Your healthcare professional will show you or your caregiver how to combine two or more vials into a larger syringe.

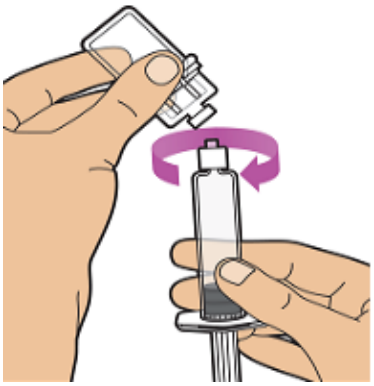
Step 14:



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

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 on the plunger rod to draw all the solution from the vial into the syringe.

Step 15

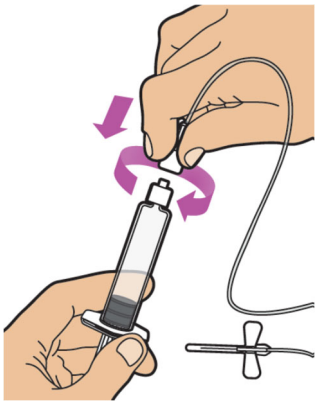


Gently unscrew the syringe from the vial adapter using a clockwise motion. Dispose of the vial with the adapter still attached. If you are not ready to inject, put the syringe cap carefully back onto the syringe tip. **Do not** touch the syringe tip or the inside of the cap.
Note: ALTUVIIIO should be administered within 3 hours after it is in solution.

ADMINISTRATION

ALTUVIIIO is given by intravenous infusion after the drug powder is in solvent. These are general instructions so your healthcare professional can teach you or your caregiver how to inject ALTUVIIIO. Once you or your caregiver have been taught to give ALTUVIIIO, you can follow these instructions. Do not give if the product in solution contains particles, is discoloured, or is cloudy.

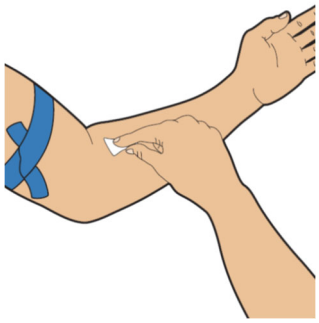
Step 16:



With clean hands in a clean area, attach the syringe to the connector end of the infusion set tubing by turning clockwise (left to right) until it is securely attached. **Do not** mix ALTUVIIIO in the same tubing or container with other drugs.

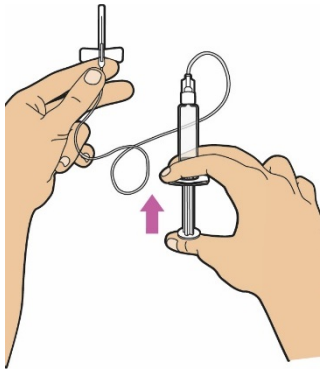
Note: Ask your healthcare professional which infusion set can be used for this product.

Step 17:



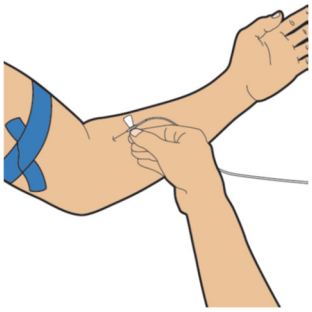
Apply a tourniquet (large elastic band) to the upper arm as trained. Then, using a new alcohol wipe, clean the skin area where you will insert the needle and wait for it to dry.

Step 18:



Fill the syringe and the tubing by pushing gently on the plunger rod until all air is removed from the syringe and ALTUVIIIO has just filled the needle. **Do not** push ALTUVIIIO through the needle.

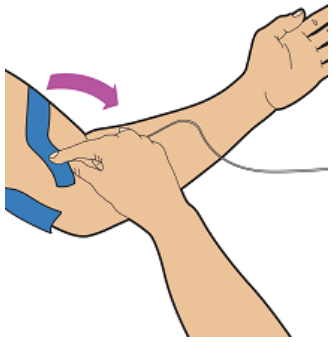
Step 19:



Remove the protective needle cover from the infusion set needle and discard it. **Do not** touch the needle (hold by plastic arms) and do not put the needle cover back onto needle after use. Insert the

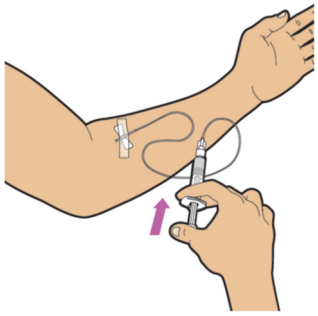
needle on the infusion set tubing into the vein as instructed by your healthcare professional. Ensure that tape is ready to secure the plastic wings of the needle later on.

Step 20:



Remove the tourniquet. Use a tape to secure the plastic wings of the needle in place at the injection site if necessary (as shown in Step 21 below).
Note: Always make sure you have correctly inserted the needle into a vein when you perform an intravenous injection.

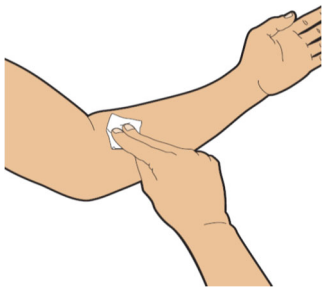
Step 21:



Slowly push the plunger rod on the syringe down to give ALTUVIIIO into the vein. Your healthcare professional will tell you or your care giver how fast to give ALTUVIIIO based on your comfort level. The time to give ALTUVIIIO will depend on how hard you or your caregiver pushes on the plunger and this may take practice under supervision.

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

Step 22:



After ALTUVIIIO is given, 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 possible bleeding.
Note: You may apply an adhesive bandage if necessary.

Step 23:

Put the infusion set, the syringe and cap, the used vial, and other used medical supplies in a puncture-resistant container right away after use. **Do not** dispose of (throw away) ALTUVIIIO in your household trash.

What are possible side effects from using ALTUVIIIO?

You can have an allergic reaction to ALTUVIIIO. Call your healthcare professional 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 professional 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 professional about any side effect that bothers you or does not go away.

If you experience any of those side effects, seek immediate medical attention.

Serious side effects and what to do about them			
Symptom / effect	**Talk to your healthcare professional**		**Stop taking drug and get immediate medical help**
	Only if severe	**In all cases**	
The following side effects could mean you are having an allergic reaction.			
Difficulty breathing			√
Chest tightness			√
Swelling of the face, rash or hives			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting Side Effects
You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada.html) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Do not use product or solvent after the expiry date that is shown on the label of the vial and the carton. Unopened vials should be stored under controlled refrigeration (2°C - 8°C). The product as a powder may be stored at room temperature up to 30°C for a single 6 month period. The date that the product is removed from refrigeration should be noted on the carton.

Do not use beyond the expiration date printed on the carton and the vial or six months after removing the carton from refrigeration, whichever is earlier.

Do not freeze. Protect from light.

The dissolved product can be stored at room temperature up to 30°C for 3 hours. Protect product from direct sunlight. After adding the solvent, if the product is not used within 3 hours, it must be thrown away.

The appearance of the dissolved product should be clear and colourless.
Do not use this medicine if you notice that it is cloudy or contains visible particles.

If you want more information about ALTUVIIIO:

- Talk to your healthcare professional.
- Find the full Product Monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website: (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website www.sanofi.com/en/canada, or by calling 1-800-265-7927.

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