Date: 20 November 2024
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Altuvoct

International non-proprietary name:	efanesoctocog alfa
Pharmaceutical form:	powder and solvent for solution for injection
Dosage strength(s):	250 IU, 500 IU, 750 IU, 1000 IU, 2000 IU, 3000 IU, 4000 IU
Route(s) of administration:	intravenous
Marketing authorisation holder:	Swedish Orphan Biovitrum AG
Marketing authorisation no.:	69436
Decision and decision date:	approved on 2 September 2024

Note:

This assessment report is as adopted by Swissmedic with all information of a commercially confidential nature deleted.

SwissPARs are final documents that provide information on submissions at a particular point in time. They are not updated after publication.

Table of contents

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental risk assessment
FDA	Food and Drug Administration (USA)
GI	Gastrointestinal
GLP	Good Laboratory Practice
HPLC	High-performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing authorisation holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PIP	Paediatric investigation plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric study plan (US FDA)
RMP	Risk management plan
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
VWF	Von Willebrand factor

2 Background information on the procedure

2.1 Applicant's request(s)

New active substance status
The applicant requested new active substance status for efanesoctocog alfa in the above-mentioned medicinal product.

Orphan drug status
The applicant requested orphan drug status in accordance with Article 4 paragraph 1 letter a^{decies} no. 2 of the TPA.
Orphan drug status was granted on 22 June 2023.

2.2 Indication and dosage

2.2.1 Requested indication

ALTUVOCT is indicated for the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency).
ALTUVOCT can be used for all age groups.

2.2.2 Approved indication

ALTUVOCT is indicated for the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency).
ALTUVOCT can be used for all age groups.

2.2.3 Requested dosage

Summary of the requested standard dosage:
The recommended dosage for routine prophylaxis in adults and children is 50 IU/kg of ALTUVOCT administered once weekly. The recommended dosage for on-demand treatment is a single dose of 50 IU/kg of ALTUVOCT. An additional dose of 30 or 50 IU/kg after 2 to 3 days may be considered. The dosage and duration of the substitution therapy depend on the severity of the factor VIII deficiency, the location and extent of the bleeding, and the clinical condition of the patient.

2.2.4 Approved dosage

(see appendix)

2.3 Regulatory history (milestones)

Application	16 June 2023
Formal control completed	30 June 2023
List of Questions (LoQ)	30 November 2023
Response to LoQ	29 January 2024
Preliminary decision	23 April 2024
Response to preliminary decision	2 June 2024
Labelling corrections	6 August 2024
Response to labelling corrections	11 August 2024
Final decision	2 September 2024
Decision	approval

3 Medical context

Haemophilia A is a rare X chromosome-linked clotting factor VIII deficiency associated with bleeding of variable severity. The worldwide prevalence of haemophilia A, based on pooling across all available national registries, has been estimated at 17.1 cases per 100,000 males [1].

Haemophilia A is a life-long disease occuring predominantly in males. Patients with severe disease experience frequent bleeding episodes into major joints, soft tissue, and muscle, either spontaneously or following even minor trauma. Repeated bleeding can lead to debilitating long-term complications, including haemophilic arthropathy.

Treatment options for patients with severe haemophilia A are still limited despite significant advances in recent years. Patients still have significant quality of life limitations and life expectancy disadvantages relative to the general population [1, 2, 3].

[1] Iorio, A, Stonebraker, JS, Chambost, H, Makris, M, Coffin, D, Herr, C et al. Establishing the Prevalence and Prevalence at Birth of Hemophilia in Males: A Meta-analytic Approach Using National Registries. Ann Intern Med. 2019;171(8):540-546.

[2] Hassan, S, Monahan, RC, Mauser-Bunschoten, EP, van Vulpen, LFD, Eikenboom, J, Beckers, EAM et al. Mortality, life expectancy, and causes of death of persons with hemophilia in the Netherlands 2001-2018. J Thromb Haemost. 2021;19(3):645-653.

[3] Hay, CRM, Nissen, F and Pipe, SW. Mortality in congenital hemophilia A - a systematic literature review. J Thromb Haemost. 2021;19 Suppl 1(Suppl 1):6-20.

4 Quality aspects

The evaluation of the quality data in this application was carried out on the basis of the previous regulatory decision by the FDA for the product marketed in the United States under the trade name ALTUVIIIO. Moreover, available assessment reports from FDA and CHMP were taken into consideration for the quality evaluation.

4.1 Drug substance

Efanesoctocog alfa is a recombinant coagulation factor VIII Fc - von Willebrand factor (VWF) - XTEN fusion protein (rFVIIIFc-VWF-XTEN) consisting of a single chain B domain deleted human FVIII covalently linked to the D'D3 domain of human VWF via the Fc domain of human immunoglobulin G1 and 2 XTEN® polypeptide (XTEN polypeptides are unstructured polypeptides consisting of repeats of 6 amino acids). The efanesoctocog alfa protein has a molecular weight of approximately 312 kDa.

Efanesoctocog alfa is produced in cells in a production bioreactor. The bulk harvest is purified through a single sequence of downstream steps which involves ultrafiltration, detergent inactivation, chromatography steps, viral filtration, and ultrafiltration.

The development of the efanesoctocog alfa drug substance manufacturing processes includes changes. The analytical comparability studies, which included batch release data, extended characterisation data, and forced degradation studies, demonstrated comparability.

The characterisation of the physicochemical and biological properties of the drug substance and its impurities were performed using state-of-the-art methods.

The specifications for the efanesoctocog alfa drug substance release and stability include relevant tests and acceptance criteria, e.g. for identity, purity and impurities, quantity, and potency. Specifications are based on clinical experience, batch analysis data, and stability data, and conform with current compendial or regulatory guidelines.

Batch analysis data of non-clinical batches, clinical batches, process performance qualification batches, and commercial batches were provided. All specific analytical methods are described and were fully validated.

During storage, no changes were observed under the proposed storage conditions. A shelf-life of 60 months has been accepted.

4.2 Drug product

Efanesoctocog alfa drug product is a sterile, lyophilised powder for solution for injection for intravenous administration. It is supplied in aseptically filled single-use vials in seven nominal strengths 250 IU, 500 IU, 750 IU, 1000 IU, 2000 IU, 3000 IU, and 4000 IU/vial.
Efanesoctocog alfa drug product is formulated at a target concentration of 83 - 1333 IU/mL of active ingredient in histidine buffer, arginine hydrochloride, sucrose, calcium chloride dihydrate, polysorbate 80. All excipients used comply with the European Pharmacopoeia. The powder for solution for injection is reconstituted in sterile water for injection supplied in a prefilled syringe at a nominal volume of 3 mL. A vial adapter, a prefilled syringe of sterile water for injection, and an infusion set are also provided with the drug product vial to facilitate administration.

During process development a new drug product manufacturing process was implemented. Comprehensive characterisation studies, release data, and forced degradation studies demonstrated comparability with respect to quantitative and qualitative critical quality attributes.
The finished product manufacturing process consists of thawing the formulated drug substance, compounding, sterile filtration, filling, lyophilisation, capping, and visual inspection steps.

The validation was shown with three consecutive process performance qualification batches of three different strengths.

The specifications for release and stability of the drug products include relevant tests and acceptance criteria, e.g. for identity, purity and impurities, quantity, potency, appearance, pH, osmolality, visible and subvisible particles, bacterial endotoxins, and sterility. The drug product specifications comply with current compendial or regulatory guidelines.

Batch analysis data for several batches of the drug products including non-clinical batches, clinical batches, and process performance qualification batches were provided. All batch release data comply with the drug product specifications. All specific analytical methods are validated.

The vials are stored at 2 – 8°C protected from light. A shelf-life of 48 months was granted.

4.3 Quality conclusions

The manufacturing processes (drug substance and drug product) are well described and demonstrate a consistent quality of drug substance and drug product. The shelf-lives of the drug substance and drug product are supported by data from recommended storage conditions, as well as accelerated and stress studies. Safety concerns with regard to viral and non-viral contaminants were satisfactorily addressed.

5 Nonclinical aspects

The Nonclinical Assessment Division conducted an abridged evaluation of the marketing authorisation application for Altuvoct, which was based on the FDA assessment report (dated 30 January 2023) retrieved from the FDA website.
Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Altuvoct in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised. There were no safety issues identified in the nonclinical studies that would be of concern for human use. All nonclinical data that are relevant for safety are adequately mentioned in the Information for healthcare professionals.

6 Clinical aspects

The evaluation of the clinical and clinical pharmacology data of this application was carried out in reliance on previous regulatory decisions by EMA and FDA. The available assessment reports and respective product information from EMA and FDA were used as a basis for the evaluation.

For further details concerning clinical pharmacology, dosing recommendations, and efficacy and safety, see the Information for healthcare professionals in the appendix to this report.

7 Risk management plan summary

The RMP summaries contain information on the medicinal products′ safety profiles and explain the measures that are taken to further investigate and monitor the risks, as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. It is the responsibility of the marketing authorisation holder to ensure that the content of the published RMP summaries is accurate and correct. As the RMPs are international documents, their summaries might differ from the content in the Information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks that occur in populations or indications not included in the Swiss authorisations.

8 Appendix

Approved Information for healthcare professionals

Please be aware that the following version of the Information for healthcare professionals for Altuvoct was approved with the submission described in the SwissPAR. This Information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the valid and relevant reference document for the effective and safe use of medicinal products in Switzerland is the Information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following Information for healthcare professionals has been translated by the MAH. It is the responsibility of the authorisation holder to ensure the translation is correct. The only binding and legally valid text is the Information for healthcare professionals approved in one of the official Swiss languages.

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

ALTUVOCT

Composition

Active substances

Efanesoctocog alfa (human coagulation factor VIII (rDNA))
Efanesoctocog alfa is a protein that has 2829 amino acids. It is produced by recombinant DNA technology in a human embryonic kidney (HEK) cell line, which has been extensively characterized.

Excipients

Powder: Sucrose, calcium chloride dihydrate, histidine, arginine hydrochloride, polysorbate 80

Solvent: Water for injections

Pharmaceutical form and active substance quantity per unit

Powder and solvent for solution for injection.
For intravenous use, after reconstitution.
1 vial of ALTUVOCT powder contains:

Dosage Strength	Nominal content of efanesoctocog alfa	Approximate concentration of efanesoctocog alpha after reconstitution [pro ml]
250 IU	250 IU	83 IU
500 IU	500 IU	167 IU
750 IU	750 IU	250 IU
1000 IU	1000 IU	333 IU
2000 IU	2000 IU	667 IU
3000 IU	3000 IU	1000 IU
4000 IU	4000 IU	1333 IU

Powder: Lyophilized, white to off-white powder or cake.
Solvent: Clear, colourless solution.

Potency assignment for ALTUVOCT is determined using an activated partial thromboplastin time (aPTT)-based one-stage clotting assay using Actin-FSL reagent. In vitro and in vivo analyses have indicated that potency was adequately assigned by the aPTT-based one-stage clotting assay, which was further confirmed by data during clinical development. The factor VIII activity of ALTUVOCT is

overestimated by the chromogenic assay and aPTT assay using Actin-FS reagent by approximately 2.5-fold.

Indications/Uses

ALTUVOCT is indicated for the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency).
ALTUVOCT can be used for all age groups.

Dosage/Administration

Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia.
After proper training in the correct injection technique (see “Additional information on reconstitution” and package leaflet), a patient may self-inject ALTUVOCT, or the patient’s caregiver may administer it, if their physician determines that it is appropriate.
To ensure traceability of biotechnological medicinal products, it is recommended that the trade name and batch number should be documented for each treatment.

Treatment monitoring

Individual patients may vary in their response to factor VIII, demonstrating different half-lives and recoveries. Dose based on bodyweight may require adjustment in underweight or overweight patients. Monitoring of factor VIII levels for the purpose of dose adjustment is usually not necessary during routine prophylaxis. In case of major surgery or life-threatening bleeds, determination of factor VIII levels is required to guide the dose and frequency of repeated injections.

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

It is recommended to use a validated one stage clotting assay to determine plasma factor VIII activity of ALTUVOCT. Throughout the clinical development an Actin-FSL-based one-stage clotting assay was used.

According to the findings of a comparative analysis of clinical study samples, results obtained using a chromogenic assay should be divided by 2.5 to approximate the patient’s factor VIII activity (see “Warnings and precautions”). In addition, a field study comparing different aPTT reagents indicated approximately 2.5-fold higher factor VIII activity levels when using Actin-FS instead of Actin-FSL in the one-stage clotting assay and approximately 30% lower results when using SynthASil.

Posology

The dose and duration of the substitution therapy depend on the severity of the factor VIII deficiency, on the location and extent of the bleeding and on the patient's clinical condition.

The number of units of factor VIII administered is expressed in International Units (IU), which are related to the current WHO concentrate standard for factor VIII products. Factor VIII activity in plasma is expressed either as a percentage (relative to normal human plasma) or preferably in International Units (relative to an International Standard for factor VIII in plasma).

One IU of factor VIII activity is equivalent to that quantity of factor VIII in one mL of normal human plasma.

For the dose of 50 IU Factor VIII/kg body weight, the expected in vivo plasma recovery in factor VIII level expressed as IU/dL (or % of normal) is estimated using the following formula:

Estimated increment of factor VIII (IU/dL or % of normal) = 50 IU/kg x 2 (IU/dL per IU/kg)

On demand treatment

ALTUVOCT dosing for the on-demand treatment, control of bleeding episodes and perioperative management is provided in Table 1.

Table 1: Guide to ALTUVOCT dosing for treatment of bleeding episodes and surgery

Degree of haemorrhage / Type of surgical procedure	**Recommended dose**	**Additional Information**
<u>Haemorrhage</u> Early haemarthrosis, muscle bleeding or oral bleeding	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. An additional dose of 30 or 50 IU/kg after 2 to 3 days may be considered.
More extensive haemarthrosis, muscle bleeding or haematoma	Single dose of 50 IU/kg	Additional doses of 30 or 50 IU/kg every 2 to 3 days may be considered until bleeding is resolved
Life Threatening haemorrhages	Single dose of 50 IU/kg	Additional doses of 30 or 50 IU/kg every 2 to 3 days may be administered until the threat is resolved
<u>Surgery</u> Minor surgery including tooth extraction	Single dose of 50 IU/kg	An additional dose of 30 or 50 IU/kg after 2 to 3 days may be considered.
<u>Major surgery</u>	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 until adequate wound healing is achieved.

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 dosing schedule.

Prophylaxis

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

Special dosage instructions

Elderly patients

There is limited experience in patients ≥ 65 years. The dosing recommendations are the same as for patients < 65 years.

Children and adolescents

The dosing recommendations are the same as for adults.
Currently available data are described in sections "Undesirable effects", "Properties/Effects" and "Pharmacokinetics".

Mode of administration

ALTUVOCT is for intravenous use.
The entire ALTUVOCT dose should be injected intravenously over 1 to 10 minutes, based on the patient's comfort level.
For instructions on dilution of the medicinal product before administration, see "Instructions for handling".

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Warnings and precautions

Hypersensitivity

Allergic type hypersensitivity reactions are possible with ALTUVOCT. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of the medicinal product immediately and contact their physician. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis.

In case of shock, standard medical treatment for shock should be implemented.

Inhibitors

The formation of neutralising antibodies (inhibitors) to factor VIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against the factor VIII pro-coagulant activity, which are quantified in Bethesda Units (BU) per ml of plasma using the modified assay. The risk of developing inhibitors is correlated to the severity of the disease as well as the exposure to factor VIII, this risk being highest within the first 50 exposure days but continues throughout life although the risk is uncommon.

The clinical relevance of inhibitor development will depend on the titre of the inhibitor, with low titres posing less of a risk of insufficient clinical response than high titre inhibitors.

In general, all patients treated with coagulation factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII inhibitor presence should be performed. In patients with high levels of inhibitor, factor VIII therapy may not be effective and other therapeutic options should be considered. Management of such patients should be directed by physicians with experience in the care of haemophilia and factor VIII inhibitors.

Monitoring laboratory tests

If the chromogenic assay or the one stage clotting assay with Actin-FS reagent are used, divide the result by 2.5 to approximate the patient's factor VIII activity level (see "Dosage/Administration"). Of note, this conversion factor only represents an estimate (mean chromogenic assay/one-stage clotting assay Actin-FSL ratio: 2.53; SD: 1.54; Q1: 1.98; Q3: 2.96; N=3 353).

Cardiovascular events

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

Catheter-related complications

If a central venous access device (CVAD) is required, risk of CVAD-related complications including local infections, bacteraemia and catheter site thrombosis should be considered.

Paediatric population

The listed warnings and precautions apply both to adults and children.

Interactions

No interactions of ALTUVOCT with other medicinal products have been reported.
No drug interaction studies have been performed.

Pregnancy, lactation

Animal reproduction studies have not been conducted with factor VIII. Based on the rare occurrence of haemophilia A in women, experience regarding the use of factor VIII during pregnancy and breast-feeding is not available. Therefore, factor VIII should be used during pregnancy and lactation only if clearly indicated.

Effects on ability to drive and use machines

ALTUVOCT has no influence on the ability to drive and use machines.

Undesirable effects

Summary of the safety profile

Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the injection site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed rarely and may in some cases progress to severe anaphylaxis (including shock).

Development of neutralising antibodies (inhibitors) may occur in patients with haemophilia A treated with factor VIII, including with ALTUVOCT (see section “Properties/effects”, “Immunogenicity”). If such inhibitors occur, the condition may manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted.

Tabulated list of adverse reactions

Table 2 presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level). Frequencies of adverse reactions are based on Phase 3 clinical studies in 277 previously treated patients (PTPs) with severe haemophilia A, of which 161 (58.2%) were adults (18 years of age and older), 37 (13.4%) were adolescents (12 to < 18 years of age), and 79 (28.5%) were children under the age of 12 years.

Adverse drug reactions (ADRs), summarized in the table below, were reported in 111 (40.1%) of the 277 subjects treated with routine prophylaxis or on-demand therapy.

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

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 2: Adverse reactions reported for ALTUVOCT in clinical trials

MedDRA System Organ Class	Adverse reactions	Frequency

Nervous system disorders	Headache[1]	Very common (15.9%)
Gastrointestinal disorders	Vomiting	Common
Skin and subcutaneous tissue disorders	Eczema	Common
	Rash[2]	Common
	Urticaria[3]	Common
Musculoskeletal and connective tissue disorders	Arthralgia	Very common (16.6%)
	Pain in extremity	Common
	Back pain	Common
General disorders and administration site conditions	Pyrexia	Common
	Injection site reaction[4]	Uncommon

[1] Headache, including migraine.
[2] Rash, including rash maculo papular.
[3] Urticaria, including urticaria papular.
[4] Injection site reaction, including injection site haematoma and injection site dermatitis.

Paediatric population

No age-specific differences in adverse reactions were observed between paediatric and adult patients.
Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

No symptoms of overdose with human coagulation factor VIII (rDNA) have been reported.

Properties/Effects

ATC code

B02BD02

Mechanism of action

Efanesoctocog alfa is replacement factor VIII therapy. Activated factor VIII acts as a cofactor for activated factor IX, accelerating the conversion of factor X to activated factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be

formed. Haemophilia A is an X-linked hereditary disorder of blood coagulation due to decreased levels of functional factor VIII:C and results in bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. By replacement therapy the plasma levels of factor VIII are increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

Of note, annualized bleeding rate (ABR) is not comparable between different factor concentrates and between different clinical studies.

ALTUVOCT (efanesoctocog alfa) or recombinant coagulation Factor VIII Fc-Von Willebrand Factor-XTEN is a recombinant fusion protein that temporarily replaces the missing coagulation Factor VIII needed for effective haemostasis.

ALTUVOCT is a FVIII protein that is designed not to bind 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.

ALTUVOCT contains 2 XTEN® polypeptides, which further increase its pharmacokinetics (PK). In ALTUVOCT, 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 is inserted in between the D'D3 domain and Fc.

Pharmacodynamics

See "Mechanism of action".

Clinical efficacy

The safety, efficacy, and pharmacokinetics of ALTUVOCT have been evaluated in two multicenter, prospective, open-label clinical studies (one study in adults and adolescents [XTEND-1] and one paediatric study in children < 12 years of age [XTEND-Kids]) in previously treated patients (PTPs) with severe haemophilia A (< 1% endogenous FVIII activity or a documented genetic mutation consistent with severe haemophilia A). The long-term safety and efficacy of ALTUVOCT is also being evaluated in a long-term extension study.

All studies evaluated the efficacy of routine prophylaxis with a weekly dose of 50 IU/kg and determined haemostatic efficacy in the treatment of bleeding episodes and during perioperative management in subjects undergoing major or minor surgical procedures. Furthermore, the efficacy of

ALTUVOCT prophylaxis compared with previous prophylactic factor VIII was also evaluated in subjects who had participated in a prospective observational study (OBS16221) prior to enrolment in the XTEND-1 study.

Clinical efficacy during routine prophylaxis in adults/adolescents

The completed adult and adolescent study (XTEND-1) enrolled a total of 159 PTPs (158 male and 1 female subjects) with severe haemophilia 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 ALTUVOCT and were evaluable for efficacy. A total of 149 subjects (93.7%) completed the study.

The efficacy of weekly 50 IU/kg ALTUVOCT as routine prophylaxis was evaluated as estimated by the mean annualized bleeding rate (ABR) (Table 3) and by comparing the ABR during on-study prophylaxis vs. the ABR during pre-study factor VIII prophylaxis (Table 4). A total of 133 adults and adolescents, who had been receiving factor VIII prophylaxis prior to study enrolment, were assigned to receive ALTUVOCT for routine prophylaxis at a dose of 50 IU/kg once weekly (QW) for 52 weeks (Arm A). An additional 26 subjects, who were on pre-study episodic (on-demand) treatment with factor VIII, received episodic (on-demand) treatment with ALTUVOCT at doses of 50 IU/kg for 26 weeks, followed by routine prophylaxis at a dose of 50 IU/kg once weekly for 26 weeks (Arm B). Overall, 115 subjects received at least a total number of 50 exposure days in Arm A and 17 subjects completed at least 25 exposure days of routine prophylaxis in Arm B.

Table 3: Summary of Annualized Bleeding Rate (ABR) with ALTUVOCT prophylaxis, ALTUVOCT on-demand treatment, and after switch to ALTUVOCT prophylaxis in subjects ≥ 12 Years of Age

Endpoint[1]	**Arm A Prophylaxis[2]**	**Arm B On demand[3]**	**Arm B Prophylaxis[3]**
	N=133	N=26	N=26
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 (IQR)	0.0 (0.0; 1.0)	21.1 (15.1; 27.1)	0.0 (0.0; 0.0)
% subjects with zero bleeds	64.7	0	76.9
Spontaneous bleeds			
Mean ABR (95% CI)[4]	0.3 (0.2; 0.4)	15.8 (12.3; 20.43)	0.4 (0.2; 1.2)
Median ABR (IQR)	0.0 (0.0; 0.0)	16.7 (8.6; 23.8)	0.0 (0.0; 0.0)
% subjects with zero bleeds	80.5	3.8	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 (IQR)	0.0 (0.0; 1.0)	18.4 (10.8; 23.9)	0.0 (0.0; 0.0)
% subjects with zero bleeds	72.2	0	80.8

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

An intra-subject comparison of ABRs during on-study and pre-study prophylaxis demonstrated a statistically significant reduction of 77% in ABR during routine prophylaxis with ALTUVOCT compared to pre-study factor VIII prophylaxis (see Table 4).

Table 4: Intra-Subject comparison of Annualized Bleeding Rate (ABR) with ALTUVOCT prophylaxis versus pre-study factor VIII prophylaxis in subjects ≥ 12 years of age

Endpoint	**On-study prophylaxis with ALTUVOCT 50 IU/kg QW (N = 78)**	**Pre-study standard of care factor VIII prophylaxis[2] (N = 78)**
Median Observation Period (weeks)(IQR)	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)
% reduction (95% CI) p-value	77 (58; 87) <0.0001	
% subjects with zero bleeds	64.1	42.3
Median ABR (IQR)	0.0 (0.0; 1.0)	1.1 (0.0; 3.7)

[1] Based on negative binomial model.
[2] Prospective observational study (OBS16221).
ABR = annualized bleed rate; CI = confidence interval; IQR = interquartile range, 25th percentile to 75th percentile.

An intra-subject comparison (N=26) of ABR during the first 26 weeks of on-demand ALTUVOCT treatment versus ABR in the following 26 weeks on weekly ALTUVOCT prophylaxis (Arm B) showed a clinically important bleeding reduction of 97% for the weekly prophylactic regimen and an increase of subjects with zero bleeds from 0 to 76.9%.

Routine prophylaxis: joint health

All subjects with target joints at baseline (defined as ≥ 3 spontaneous bleeding episodes in a major joint which occurred in a consecutive 6-month period) achieved resolution of all target joints (45/45, 100%) with 12 months of prophylactic treatment with ALTUVOCT (defined as ≤ 2 bleeding episodes in the target joint in 12 months).

Efficacy in control of bleeding

In the adult and adolescent study (XTEND-1), a total of 362 bleeding episodes were treated with ALTUVOCT, most occurring during on-demand treatment in Arm B. The majority of bleeding episodes were localized in joints. Response to the first injection was assessed by subjects at least 8 hours after treatment. A 4-point rating scale of excellent, good, moderate, and no response was used to assess

response. Bleeding was resolved with a single 50 IU/kg injection of ALTUOCT in 96.7% of bleeding episodes. The median (Q1; Q3) total dose to treat a bleeding episode was 50.9 IU/kg (50.0; 51.9). Efficacy in control of bleeding episodes in subjects ≥ 12 years of age is summarized in Table 5. Control of bleeding episodes was similar across the treatment arms.

Table 5: Summary of efficacy in control of bleeding in subjects ≥ 12 years of age

Number of bleeding episodes		**(n=362)**
Number of injections to treat bleeding episode, n (%)	1 Injection 2 Injections > 2 Injections	350 (96.7) 11 (3.0) 1 (0.3)
Median total dose to treat a bleeding episode (IU/kg) (IQR)		50.93 (50.00; 51.85)
Number of evaluable injections		**(n=332)**
Response to treatment of a bleeding episode, n (%)	Excellent or good Moderate No response	315 (94.9) 14 (4.2) 3 (0.9)

Perioperative management of bleeding

Major surgeries

Perioperative haemostasis was assessed in 49 major surgeries in 41 subjects (32 adults and 9 adolescents and children) across Phase 3 studies. Of the 49 major surgeries, 48 surgeries required a single pre-operative dose to maintain haemostasis during surgery; for 1 major surgery during routine prophylaxis, no pre-operative loading dose was administered on the day of/or before surgery. The median dose per pre-operative injection was 50 IU/kg (range 12.7 - 84.7). The mean (SD) total consumption and number of injections during the perioperative period (from the day before surgery until Day 14 after surgery) were 171.85 (51.97) IU/kg and 3.9 (1.4), respectively.

The clinical evaluation of haemostatic response during major surgery was assessed using a 4-point scale of excellent, good, moderate, or poor/none. The haemostatic effect of ALTUVOCT was rated as “excellent” or “good” in 48 of 49 surgeries (98%). No surgery had an outcome rated as “poor/none” or “missing.”

Types of major surgeries assessed include 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, dental restoration and tooth extraction, circumcision, resection of vascular malformation, hernia repair, and rhinoplasty/mentoplasty.

Minor surgeries

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

Immunogenicity

Immunogenicity was evaluated during clinical trials with ALTUVOCT in previously treated adults and children diagnosed with severe haemophilia A. Inhibitor development to ALTUVOCT was not detected in clinical trials.

During Phase 3 clinical studies (median treatment duration 96.3 weeks), 4/276 (1.4%) of evaluable patients developed transient treatment-emergent anti-drug antibodies (ADA). No evidence of ADA impact on pharmacokinetics, efficacy or safety was observed.

Paediatrics

Routine prophylaxis

The efficacy of weekly 50 IU/kg ALTUVOCT as routine prophylaxis in children < 12 years was evaluated as estimated by the mean ABR. A total of 74 children (38 children < 6 years of age and 36 children 6 to < 12 years of age) were enrolled to receive ALTUVOCT for routine prophylaxis at a dose of 50 IU/kg intravenously once weekly for 52 weeks. In all 74 subjects, routine prophylaxis resulted in an overall mean ABR (95% CI) of 0.9 (0.6; 1.4) and a median (Q1; Q3) ABR of 0 (0; 1.0) for treated bleeds.
A sensitivity analysis (N = 73), excluding one subject who did not receive the weekly prophylaxis treatment as specified in the protocol for an extended period, showed a mean ABR (95% CI) of 0.6 (0.4; 0.9) for treated bleeds [median (Q1; Q3) 0 (0; 1.0)]. 47 children (64.4%) experienced no bleeding episode that required treatment. The mean ABR (95% CI) for treated spontaneous bleeds was 0.2 (0; 0.3) [median (Q1; Q3) 0 (0; 0)]. For treated joint bleeds, the mean ABR (95% CI) was 0.3 (0.2; 0.6) and the median (Q1; Q3) was 0 (0; 0).

Control of bleeding

The efficacy in control of bleeding in children < 12 years of age was assessed in the paediatric study, excluding one subject who did not receive the weekly prophylaxis treatment as specified in the protocol for an extended period. A total of 43 bleeding episodes were treated with ALTUVOCT. Bleeding was resolved with a single 50 IU/kg injection of ALTUVOCT in 95.3% of bleeding episodes. The median (Q1; Q3) total dose to treat a bleeding episode was 52.6 IU/kg (50.0; 55.8).

Pharmacokinetics

Absorption

See “Elimination”.

Distribution

See “Elimination”.

Metabolism

See “Elimination”.

Elimination

The pharmacokinetics (PK) of ALTUVOCT were evaluated in the Phase 3 studies XTEND-1 and XTEND-Kids, enrolling 159 adults and adolescents, and 74 children < 12 years old, respectively, receiving weekly IV injections of 50 IU/kg. Among children < 12 years old, 37 subjects had ALTUVOCT single dose PK profiles available.

Efanesoctocog alfa has demonstrated a half-life that is about 4-fold longer compared to standard half-life factor VIII products and about 2.5- to 3-fold longer compared to extended half-life factor VIII products. PK parameters following a single dose of ALTUVOCT are presented in Table 6. The PK parameters were based on plasma factor VIII activity measured by the aPTT-based one-stage clotting assay. After a single dose of 50 IU/kg, ALTUVOCT exhibited high sustained factor VIII activity with prolonged half-life across age cohorts. There was a trend of increasing AUC, and decreasing clearance, with increasing age in the paediatric cohorts. The PK profile at steady state (week 26) was comparable with the PK profile after the first dose.

Table 6: Pharmacokinetic parameters following a single dose of ALTUVOCT by age (one-stage clotting assay)

PK parameters (mean SD)	**Paediatric 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**
$AUC_{0\text{-}tau}$, IU*h/dl	6800 (1120)[b]	7190 (1450)	8350 (1550)	9850 (2010)[a]
$t_{1/2z}$, h	38.0 (3.72)	42.4 (3.70)	44.6 (4.99)	48.2 (9.31)
CL, ml/h/kg	0.742 (0.121)	0.681 (0.139)	0.582 (0.115)	0.493 (0.121)[a]
V_{ss}, ml/kg	36.6 (5.59)	38.1 (6.80)	34.9 (7.38)	31.0 (7.32)[a]
MRT, h	49.6 (5.45)	56.3 (5.10)	60.0 (5.54)	63.9 (10.2)[aFehler! Textmarke nicht definiert.]
C_{max}, IU/dl	143 (57.8)	113 (22.7)	118 (24.9)	133 (33.8)
Incremental Recovery, IU x h/dl per IU/kg	2.81 (1.1)	2.24 (0.437)	2.34 (0.490)	2.64 (0.665)

[a] Calculation based on 128 profiles.
[b] N=17

$AUC_{0\text{-}tau}$ = 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, C_{max} = maximum activity

ALTUVOCT at steady state maintained normal to near normal (>40 IU/dL) factor VIII 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 adolescent subjects throughout the study. In children < 12 years, weekly ALTUVOCT at steady state maintained normal to near normal (>40 IU/dL) factor VIII activity for 2 to 3 days and >10 IU/dL factor VIII activity for approximately 7 days (see Table 7).

Table 7: Pharmacokinetic parameters at steady state of ALTUVOCT by age (one stage clotting assay)

PK parameters Mean (SD)	**Paediatric study[a]**		**Adult and Adolescent study[a]**	
	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) (N=35)	131 (36.1) (N=35)	124 (31.2)	150 (35.0) (N=124)
IR, kg*IU/dLper IU	2.22 (0.83) (N=35)	2.10 (0.73) (N=35)	2.25 (0.61) (N=22)	2.64 (0.61) (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	115 (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) (N=123)

[a] Steady state peak, trough and IR were computed using available measurements at week 52/end of study PK sampling visit.
[b] Time to factor VIII activity (equal to the time period, during which the factor VIII activity is above the declared value) was predicted using population PK model for paediatric patients.
[c] Time to factor VIII activity (equal to the time period, during which the factor VIII activity is above the declared value) was predicted using a population PK model for adult patients.
Peak = 15 min post dose at steady state, IR = incremental recovery, Trough = predose factor VIII activity value at steady state, SD = standard deviation

Specific Populations

The following factors have no clinically meaningful effect on the pharmacokinetics of ALTUVOCT: age (1.4 to 72 years), sex, race (White, Asian), VWF antigen activity (40 to 339 IU/dL), haematocrit level (28% to 57%), blood type, HCV status, or HIV status. Body weight (12.5 to 133 kg) is expected to alter weight normalised clearance (dL/h/kg) by 79% to -18% compared to a typical patient.

Preclinical data

Non-clinical data reveal no special hazard for humans based on repeated dose toxicity studies in rats and monkeys. Studies to investigate the genotoxicity, the carcinogenic potential, the reproductive toxicity or the embryo-fetal developmental toxicity have not been conducted.

Other information

Incompatibilities

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

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Unopened vial (before reconstitution)

During the shelf-life, the product may be stored at room temperature (up to 30°C) for a single period not exceeding 6 months. The date that the product is removed from refrigeration should be recorded on the carton. After storage at room temperature, the product may not be returned to the refrigerator. Do not use beyond the expiration date printed on the vial or six months after removing the carton from refrigeration, whichever is earlier.

Shelf life after reconstitution

The reconstituted preparation for injection is not preserved.
The product should be used immediately after reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

Special precautions for storage

Store in the refrigerator (2-8°C).
Do not freeze.
Keep the container in the outer carton in order to protect the contents from light.
Keep out of the reach of children.
For storage conditions after reconstitution of the medicinal product, see “Shelf life after reconstitution”.

Instructions for handling

ALTUVOCT is to be administered intravenously after reconstitution of the powder with the solvent supplied in the syringe. The vial should be gently swirled until all of the powder is dissolved. After reconstitution the solution should be clear and colourless to slightly opalescent. Do not use solutions that are cloudy or have deposits.

Always use an aseptic technique.

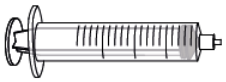
Additional information on reconstitution

ALTUVOCT is administered by intravenous (IV) injection after dissolving the powder for injection with the solvent supplied in the pre-filled syringe. ALTUVOCT pack contains:

				
A. Powder vial	B. 3 ml syringe (pre-filled with solvent)	C. Plunger rod	D. Vial adapter	E. Infusion set

You will also need sterile alcohol swabs (F). This device is not included in the ALTUVOCT package.

To draw up the solution from multiple vials into a single syringe you may use a separate large syringe (G). If a large syringe is not available, follow steps 6 to 8 to administer the solution from each syringe.

	
F. Alcohol swabs	G. Large syringe

ALTUVOCT should not be mixed with other solutions for injection or infusion.

Wash your hands before opening the pack.

Reconstitution

1. Prepare the vial

a. **Remove the vial cap**

Hold the powder vial (A) on a clean flat surface and remove the plastic cap.

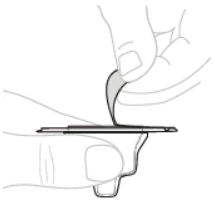
b. **Clean vial top**

Wipe the top of the vial with an alcohol swab (F).
After cleaning, ensure nothing touches the top of the vial.

c. **Open vial adapter package**

Peel off the protective paper lid from the vial adapter package (D).

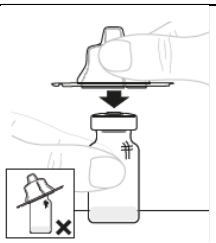
Do not touch the vial adapter or remove it from its package.



d. **Attach vial adapter**

Place the vial adapter package squarely over the top of the vial.

Press down firmly until the adapter snaps into place. The spike will penetrate the vial stopper.



2. Prepare the syringe

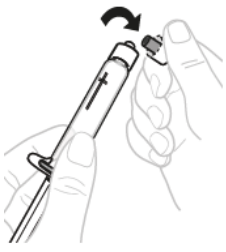
a. **Attach plunger rod**

Insert the plunger rod (C) into the 3 ml syringe (B). Turn the plunger rod clockwise until it is securely attached.

b. **Remove syringe cap**

Snap off the top part of white 3 ml syringe cap at the perforations and set aside.

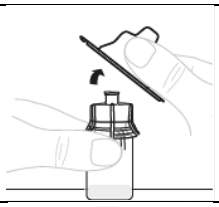
⚠ **Do not touch the inside of cap or the syringe tip.**



3. Attach syringe to vial

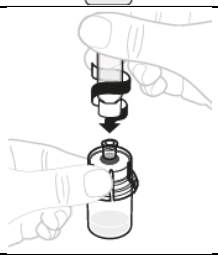
a. **Remove vial adapter package**

Lift the package away from the vial adapter and dispose.



b. Attach syringe to vial adapter

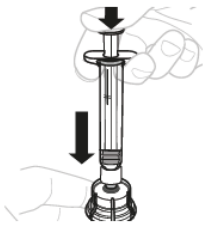
Hold the vial adapter at the lower end. Place the syringe tip onto the top of the vial adapter. Turn the syringe clockwise to securely attach.



4. Dissolve the powder and solvent

a. **Add solvent to vial**

Slowly press the plunger rod to inject all the solvent into the vial.



b. **Dissolve powder**

With your thumb on the plunger rod, gently swirl the vial until powder is dissolved.

Do not shake.

c. **Inspect solution**

Inspect the solution before administration. It should be clear and colourless.

Do not use the solution if cloudy or contains visible particles.

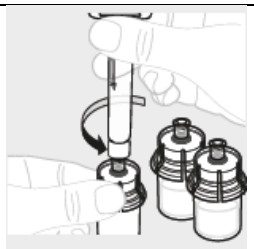
5. If using multiple vials

If your dose requires multiple vials, follow the steps below (5a and 5b) otherwise skip to step 6.

a. **Repeat 1 to 4**

Repeat steps 1 to 4 with all vials until you have prepared enough solution for your dose.

Remove the 3 ml syringes from each vial (see step 6b), leaving the solution in each vial.



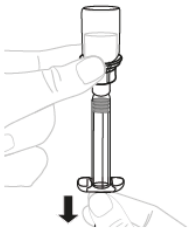
b. **Using large syringe (G)**

For each vial, attach the large syringe (G) to the vial adapter (see step 3b) and perform step 6, to combine the solution from each vial into the large syringe. In case you only need part of an entire vial, use the scale on the syringe to see how much solution you withdraw.

6. Draw solution into syringe

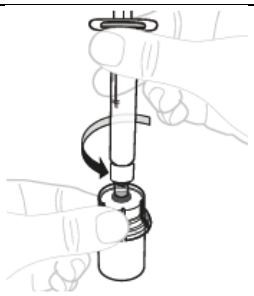
a. **Draw back solution**

Point the syringe up. Slowly pull the plunger rod to draw all the solution into the syringe.



b. **Detach syringe**

Detach the syringe from the vial by holding the vial adapter. Turn the syringe anticlockwise to detach.



ALTUVOCT should be used immediately after reconstitution.

Administration

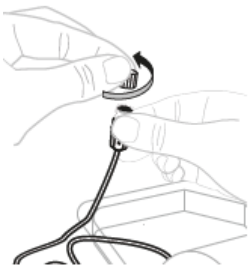
7. Prepare for injection

a. **Remove tubing cap**

Open infusion set (E) packaging (do not use if damaged).

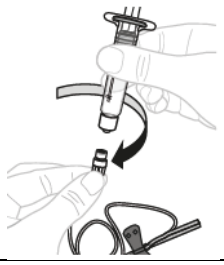
Remove the tubing cap.

⚠ **Do not touch the exposed end of the tubing set.**



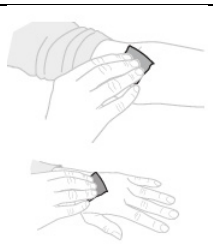
b. **Attach syringe**

Attach prepared syringe to the end of the infusion set tubing by turning the syringe clockwise.



c. **Prepare injection site**

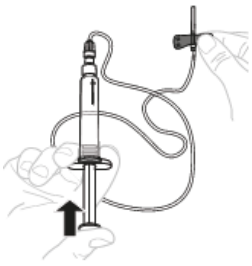
If needed apply a tourniquet. Wipe injection site with an alcohol swab (F).



d. **Remove air from syringe and tubing**

Remove air by pointing the syringe up and gently pressing the plunger rod. Do not push the solution through the needle.

⚠ **Injecting air into the vein can be dangerous.**



8. Inject solution

a. **Insert needle**

Remove protective needle cover.

Insert the needle into a vein and remove the tourniquet if used.

❗ You may use a plaster to hold the plastic wings of the needle in place at the injection site to prevent movement.

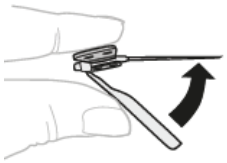
b. **Inject solution**

The prepared solution should be injected intravenously over 1 to 10 minutes, based on the patient's comfort level.

9. Dispose safely

a. **Remove needle**

Remove the needle. Fold over the needle protector; it should snap into place.



b. **Safe disposal**

Ensure all used components of the provided kit (other than packaging) are safely disposed of in a medical waste container.

⚠ **Do not reuse equipment.**

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

Authorisation number

69436 (Swissmedic)

Packs

ALTUVOCT powder and solvent for solution for injection is available in packs of 250, 500, 750, 1000, 2000, 3000 or 4000 IU.

Each pack of ALTUVOCT contains**:**

- 1 glass vial with white to off-white powder or cake
- 1 pre-filled glass syringe with 3 ml of clear, colourless solvent
- 1 sterile vial adapter for reconstitution
- 1 plunger rod
- 1 sterile infusion set

[B]

Marketing authorisation holder

Swedish Orphan Biovitrum AG, Basel

Date of revision of the text

April 2024