SUMMARY OF PRODUCT CHARACTERISTICS

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

1 NAME OF THE MEDICINAL PRODUCT

ALTUVOCT 1 000 IU powder and solvent for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains nominally 1 000 IU efanesoctocog alfa. ALTUVOCT contains approximately 333 IU/mL of human coagulation factor VIII efanesoctocog alfa after reconstitution.

Potency is determined using an activated partial thromboplastin time (aPTT)-based one-stage clotting assay with Actin-FSL reagent.

Efanesoctocog alfa [human coagulation factor VIII (rDNA)] is a protein that has 2 829 amino acids.

Efanesoctocog alfa is produced by recombinant DNA technology in a human embryonic kidney (HEK) cell line. No raw materials of human or animal origin are used in the manufacturing process.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Powder: lyophilized, white to off-white powder or cake

Solvent: clear, colourless solution

pH: 6.5 to 7.2

Osmolality: 586 to 688 mOsm/kg

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment and prophylaxis of bleeding in patients 2 years and above with severe or moderate haemophilia A (≤ 5% endogenous plasma factor VIII activity).

4.2 Posology and method of administration

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

After proper training in the correct injection technique (see section 6.6 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.

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 plasma factor VIII activity 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 plasma factor VIII activity 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 plasma factor VIII activity (see section 4.4). In addition, a field study comparing different aPTT reagents indicated approximately 2.5-fold higher plasma 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 per 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
Haemorrhage		
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.
Surgery		
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.
Major surgery	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 populations

Elderly

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

Paediatric population

The dosing recommendations are the same as for adults. There is limited data in paediatric patients < 2 years of age.

ALTUVOCT should not be used in children below 2 years of age.

Method of administration

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 section 6.6.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Traceability

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

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 levels of plasma factor VIII activity 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 inhibitors, factor VIII therapy may not be effective. In patients with high titre inhibitors, 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 plasma factor VIII activity level (see section 4.2). 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.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions of human coagulation factor VIII (rDNA) products with other medicinal products have been reported.

No interaction studies have been performed.

4.6 Fertility, pregnancy and 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.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the injection site, chills, flushing, 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 5.1). 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 Table 2) 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 to <1/10); uncommon (≥1/1 000 to <1/100); rare (≥1/10 000 to <1/1 000); very rare (<1/10 000), not known (cannot be estimated from the available data).

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

Table 2: Adverse reactions reported for ALTUVOCT in clinical studies

MedDRA system organ class	Adverse reactions	Frequency category
Nervous system disorders	Headache[1]	Very common
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
	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 of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme

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

4.9 Overdose

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

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihaemorrhagics, blood coagulation factor VIII, 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.

Efanesoctocog alfa 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.

Efanesoctocog alfa contains 2 XTEN polypeptides, which further increase its pharmacokinetics (PK). 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.

Clinical efficacy and safety

The safety, efficacy, and pharmacokinetics of ALTUVOCT have been evaluated in two multi-centre, prospective, open-label Phase 3 clinical studies (one study in adults and adolescents [XTEND-1] and one paediatric study in children < 12 years of age [XTEND-Kids, see Paediatric population]) 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 an on-going long-term extension study.

Refer to the UK Public Assessment Report on the MHRA website for additional information on the clinical studies submitted to support ALTUVOCT.

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.

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). 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

Endpoint[1]	Arm A Prophylaxis[2]	Arm B On demand[3]	Arm B Prophylaxis[3]
Bleeds			
Mean ABR (95% CI)[4]	0.71 (0.52; 0.97)	21.41 (18.81; 24.37)	0.70 (0.33; 1.49)
Median ABR (IQR)	0.00 (0.00; 1.04)	21.13 (15.12; 27.13)	0.00 (0.00; 0.00)
Subjects with zero bleeds, %	64.7	0	76.9
Spontaneous bleeds			
Mean ABR (95% CI)[4]	0.27 (0.18; 0.41)	15.83 (12.27; 20.43)	0.44 (0.16; 1.20)
Median ABR (IQR)	0.00 (0.00; 0.00)	16.69 (8.64; 23.76)	0.00 (0.00; 0.00)
Subjects with zero bleeds, %	80.5	3.8	84.6
Joint bleeds			
Mean ABR (95% CI)[4]	0.51 (0.36; 0.72)	17.48 (14.88; 20.54)	0.62 (0.25; 1.52)
Median ABR (IQR)	0.00 (0.00; 1.02)	18.42 (10.80; 23.90)	0.00 (0.00; 0.00)
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.

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. Efficacy in control of bleeding episodes in subjects ≥ 12 years of age is summarized in Table 4. Control of bleeding episodes was similar across the treatment arms.

Table 4: Summary of efficacy in control of bleeding in subjects ≥ 12 years of age

Number of bleeding episodes	(N = 362)

Number of bleeding episodes		**(N = 362)**
Number of injections to treat bleeding episode, N (%)	1 injection	350 (96.7)
	2 injections	11 (3.0)
	> 2 injections	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	315 (94.9)
	Moderate	14 (4.2)
	No response	3 (0.9)

Immunogenicity

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

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.

Paediatric population

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 (2 children < 2 years of age, 36 children 2 to < 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.

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).

5.2 Pharmacokinetic properties

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 intravenous 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 5. 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 obtained after the first dose.

Table 5: Pharmacokinetic parameters following a single dose of ALTUVOCT by age (one-stage clotting assay using Actin-FSL)

PK parameters Mean (SD)	**Paediatric study**		**Adult and adolescent study**	
	1 to < 6 years	**6 to < 12 years**	**12 to < 18 years**	**Adults**
	N = 18	**N = 18**	**N = 25**	**N = 134**
$AUC_{0\text{-}tau}$, IU*h/dL	6 800 (1 120)[b]	7 190 (1 450)	8 350 (1 550)	9 850 (2 010)[a]
$t_{½z}$, 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)[a]
C_{max}, IU/dL	143 (57.8)[c]	113 (22.7)	118 (24.9)	133 (33.8)
Incremental Recovery, IU/dL per IU/kg	2.81 (1.1)[c]	2.24 (0.437)	2.34 (0.490)	2.64 (0.665)

[a] Calculation based on 128 profiles.

[b] N = 17

[c] N = 19

$AUC_{0\text{-}tau}$ = area under the activity-time curve over the dosing interval, CL = clearance, MRT = mean residence time, SD = standard deviation, $t_{½z}$ = terminal half-life, V_{ss} = volume of distribution at steady state, C_{max} = maximum activity

In XTEND-1, 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 factor VIII 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 6).

Table 6: Pharmacokinetic parameters at steady state of ALTUVOCT by age (one-stage clotting assay using Actin-FSL)

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)
Incremental Recovery, IU/dL per IU/kg	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	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) (N = 123)

[a] Steady state peak, trough and incremental recovery were computed using available measurements at week 52/end of study PK sampling visit.

[b] Time to factor VIII activity was predicted using a population PK model for paediatric patients.

[c] Time to factor VIII activity was predicted using a population PK model for adult patients.

Peak = 15 min post dose at steady state, Trough = predose factor VIII activity value at steady state, SD = standard deviation

The indication for treatment and prophylaxis of patients with moderate haemophilia A is based on a modelling exercise.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on repeated dose toxicity studies in rats and monkeys (including measurements of safety pharmacology) and an *in vitro* haemocompatibility study. Studies to investigate genotoxicity,

carcinogenicity toxicity to reproduction or embryo-foetal development have not been conducted.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

Sucrose

Calcium chloride dihydrate (E 509)

Histidine

Arginine hydrochloride

Polysorbate 80 (E 433)

Solvent

Water for injections

6.2 Incompatibilities

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

Only the provided adapter and infusion set should be used because treatment failure can occur as a consequence of coagulation factor VIII adsorption to the internal surface of some injection equipment.

6.3 Shelf life

Unopened vial

4 years

During the shelf-life, the medicinal product may be stored at room temperature (up to 30 °C) for a single period not exceeding 6 months. The date that the medicinal

product is removed from refrigeration should be recorded on the carton. After storage at room temperature, the medicinal product may not be returned to the refrigerator. Do not use beyond the expiry date printed on the vial or six months after removing the carton from refrigeration, whichever is earlier.

After reconstitution

The medicinal 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.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

Do not freeze.

Keep the vial in the outer carton in order to protect from light.

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

6.5 Nature and contents of container

Each pack of ALTUVOCT 1 000 IU powder and solvent for solution for injection contains:

- a glass vial (type I) with powder and chlorobutyl rubber stopper
- a sterile vial adapter for reconstitution
- a pre-filled glass syringe of 3 mL solvent with a bromobutyl rubber plunger stopper
- a plunger rod
- a sterile infusion set

6.6 Special precautions for disposal

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 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 solvent in pre-filled syringe

C. Plunger rod

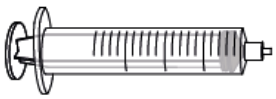
D. Vial adaptor

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.

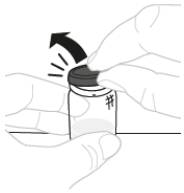
Wash your hands before opening the pack.

Reconstitution

1. <u>Prepare the vial</u>

a. **Remove the vial cap**

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



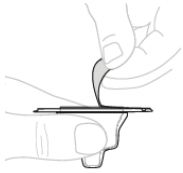
b. **Clean vial top**

Wipe the top of the vial with an alcohol swab.

After cleaning, ensure nothing touches the top of the vial.

c. **Open vial adapter package**

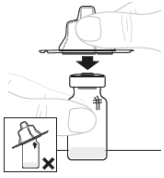
Peel off the protective paper lid from the vial adapter package (D).



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.



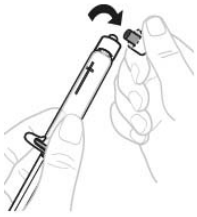
Press down firmly until the adapter snaps into place. The spike will penetrate the vial stopper.

2. <u>Prepare the syringe</u>

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**

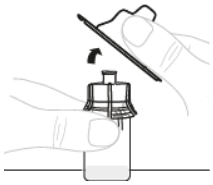


Snap off the top part of white 3 mL syringe cap at the perforations and set aside.

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

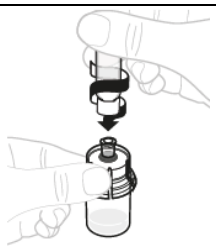
3. <u>Attach syringe to vial</u>

a. **Remove vial adapter package**



Lift the package away from the vial adapter and dispose.

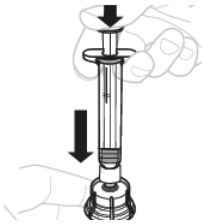
b. **Attach syringe to vial adapter**



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. <u>Dissolve the powder and solvent</u>

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**

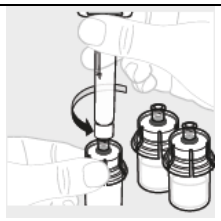
Inspect the solution before administration. It should be clear and colourless.

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

5. <u>If using multiple vials</u>

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.

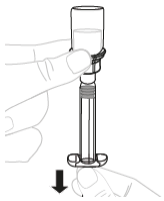
Remove the 3 mL syringes from each vial (see step 6b), leaving the solution in each vial.

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.

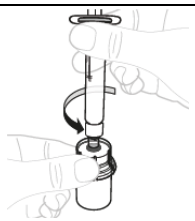
6. <u>Draw solution into syringe</u>

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.

It is recommended to use ALTUVOCT immediately after reconstitution (see section 6.3).

Administration

7. <u>Prepare for injection</u>

a. **Remove tubing cap**

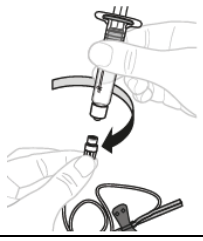
Open infusion set (E) packaging (do not use if damaged).

Remove the tubing cap

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

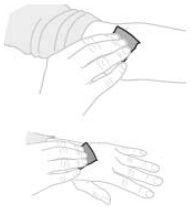
b. **Attach syringe**

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



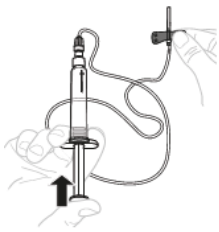
c. **Prepare injection site**

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. <u>Inject solution</u>

a. **Insert needle**

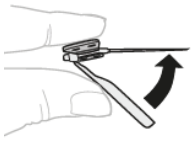
Remove protective needle cover.

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. <u>Dispose safely</u>
a. **Remove needle** Remove the needle. Fold over the needle protector; it should snap into place. 
b. Safe disposal Ensure all used components in the provided kit (other than packaging) is safely dispose 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.

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