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SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

ELOCTA 3000 IU powder and solvent for solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains nominally 3000 IU efmoroctocog alfa. ELOCTA contains approximately 1000 IU/mL of recombinant efmoroctocog alfa after reconstitution.

The potency (International Units (IU)) is determined using the European Pharmacopoeia chromogenic assay. The specific activity of ELOCTA is 4000-10200 IU/mg protein.

Efmoroctocog alfa (recombinant human coagulation factor VIII, Fc fusion protein (rFVIIIFc)) has 1,890 amino acids. It is produced by recombinant DNA technology in a human embryonic kidney (HEK) cell line without the addition of any exogenous human- or animal-derived protein in the cell culture process, purification or final formulation.

Excipient with known effect

0.6 mmol (or 14 mg) sodium per vial.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Powder: lyophilised, white to off-white powder or cake.

Solvent: water for injections, a clear, colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency).

ELOCTA can be used for all age groups.

4.2 Posology and method of administration

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

Treatment monitoring

During the course of treatment, appropriate determination of factor VIII levels (by one-stage clotting or chromogenic assays) is advised to guide the dose to be administered and the frequency of repeated injections. 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 and overweight patients. In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of coagulation analysis (plasma factor VIII activity) is indispensable.

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 the 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 reagent used in the assay.

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

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

On-demand treatment

The calculation of the required dose of recombinant factor VIII Fc is based on the empirical finding that 1 IU factor VIII per kg body weight raises the plasma factor VIII activity by 2 IU/dL. The required dose is determined using the following formula:

Required units = body weight (kg) × desired factor VIII rise (%) (IU/dL) × 0.5 (IU/kg per IU/dL)

The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case.

In the case of the following haemorrhagic events, the factor VIII activity should not fall below the given plasma activity level (in % of normal or IU/dL) in the corresponding period. Table 1 can be used to guide dosing in bleeding episodes and surgery:

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

Degree of haemorrhage / Type of surgical procedure	Factor VIII level required (%) (IU/dL)	Frequency of doses (hours)/ Duration of therapy (days)
Haemorrhage		
Early haemarthrosis, muscle bleeding or oral bleeding	20-40	Repeat injection every 12 to 24 hours for at least 1 day, until the bleeding episode as indicated by pain is resolved or healing is achieved. [1]
More extensive haemarthrosis, muscle bleeding or haematoma	30-60	Repeat injection every 12 to 24 hours for 3-4 days or more until pain and acute disability are resolved. [1]
Life threatening haemorrhages	60-100	Repeat injection every 8 to 24 hours until threat is resolved.
Surgery		
Minor surgery including tooth extraction	30-60	Repeat injection every 24 hours, for at least 1 day, until healing is achieved.
Major surgery	80-100 (pre- and post-operative)	Repeat injection every 8 to 24 hours as necessary until adequate wound healing, then therapy at least for another 7 days to maintain a factor VIII activity of 30% to 60% (IU/dL).

[1] In some patients and circumstances the dosing interval can be prolonged up to 36 hours. See section 5.2 for pharmacokinetic data.

Prophylaxis

For long term prophylaxis, the recommended dose is 50 IU of factor VIII per kg body weight at intervals of 3 to 5 days. The dose may be adjusted based on patient response in the range of 25 to 65 IU/kg (see section 5.1 and 5.2).

In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.

Elderly

There is limited experience in patients ≥65 years.

Paediatric population

For children below the age of 12, more frequent or higher doses may be required (see section 5.1). For adolescents of 12 years of age and above, the dose recommendations are the same as for adults.

Method of administration

ELOCTA is for intravenous use.

ELOCTA should be injected intravenously over several minutes. The rate of administration should be determined by the patient's comfort level and should not exceed 10 mL/min.

For instructions on reconstitution 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

Hypersensitivity

Allergic type hypersensitivity reactions are possible with ELOCTA. 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 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 procoagulant 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 titre 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.

Cardiovascular events

In patients with existing cardiovascular risk factors, substitution therapy with FVIII 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.

Traceability

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

Paediatric population

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

Excipient related considerations

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially ‘sodium-free’.

However, depending on the body weight and posology, the patient could receive more than one vial (see section 2 for information on content per vial). This should be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions of human coagulation factor VIII (rDNA) 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. A placental transfer study in mice was conducted with ELOCTA (see section 5.3). 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 breast-feeding only if clearly indicated.

4.7 Effects on ability to drive and use machines

ELOCTA has no 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 infusion 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 ELOCTA. If such inhibitors occur, the condition will 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
The Table 2 presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level). Frequencies of adverse reactions are based on clinical studies with a total of 379 patients with severe haemophilia A, of which 276 were previously treated patients (PTPs) and 103 were previously untreated patients (PUPs). See section 5.1 for additional details on the clinical studies.

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 ELOCTA in clinical trials[1]

MedDRA System Organ Class	Adverse reactions	Frequency category[1]
Blood and lymphatic system disorders	FVIII inhibition	Uncommon (PTPs)[2] Very common (PUPs)[2]
Nervous system disorders	Headache	Uncommon
	Dizziness	Uncommon
	Dysgeusia	Uncommon
Cardiac disorders	Bradycardia	Uncommon
Vascular disorders	Hypertension	Uncommon
	Hot flush	Uncommon
	Angiopathy[4]	Uncommon
Respiratory, thoracic, and mediastinal disorders	Cough	Uncommon
Gastrointestinal disorders	Abdominal pain, lower	Uncommon
Skin and subcutaneous tissue disorders	Papular rash	Common (PUPs)[3]
	Rash	Uncommon
Musculoskeletal and connective tissue disorders	Arthralgia	Uncommon
	Myalgia	Uncommon
	Back pain	Uncommon
	Joint swelling	Uncommon
General disorders and administration site conditions	Device related thrombosis	Common (PUPs)[3]
	Malaise	Uncommon
	Chest pain	Uncommon
	Feeling cold	Uncommon
	Feeling hot	Uncommon
Injury, poisoning, and procedural complications	Procedural hypotension	Uncommon

PTPs= previously treated patients, PUPs= previously untreated patients.

[1] ADRs and frequency are based on occurrence in PTPs only, unless otherwise noted.

[2]Frequency is based on studies with all FVIII products which included patients with severe haemophilia A.

[3]ADRs and frequency are based on occurrence in PUPs only.

[4] Investigator term*: vascular pain after injection of ELOCTA*

Paediatric population

No age-specific differences in adverse reactions were observed between paediatric and adult subjects. Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

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 have been reported.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihaemorrhagics, blood coagulation factor VIII, ATC code: B02BD02

Mechanism of action
The factor VIII/von Willebrand factor complex consists of two molecules (factor VIII and von Willebrand factor) with different physiological functions. When infused into a haemophiliac patient, factor VIII binds to von Willebrand factor in the patient's circulation. 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.

ELOCTA (efmoroctocog alfa) is a fully recombinant fusion protein with extended half-life. ELOCTA is comprised of recombinant B-domain deleted human coagulation factor VIII covalently linked to the Fc domain of human immunoglobulin G1. The Fc region of human immunoglobulin G1 binds to the neonatal Fc receptor. This receptor is expressed throughout life and is part of a naturally occurring pathway that protects immunoglobulins from lysosomal degradation by cycling these proteins back into circulation, resulting in their long plasma half-life. Efmoroctocog alfa binds to neonatal Fc receptor thereby utilising this same naturally occurring pathway to delay lysosomal degradation and allow for longer plasma half-life than endogenous factor VIII.

Clinical efficacy and safety

The safety, efficacy, and pharmacokinetics of ELOCTA in previously treated patients (PTPs) were evaluated in 2 multinational, open-label, pivotal phase 3 studies, Study I and Study II (see Paediatric population), and an extension study (Study III) with a duration of up to four years. In total 276 PTPs were followed for a total of 80,848 exposure days with a median of 294 (range 1-735) exposure days per patient. In addition, a phase 3 study (Study IV) was performed to evaluate the safety and efficacy of ELOCTA in previously untreated patients (PUPs) (see Paediatric population).

Study I enrolled 165 previously treated male patients (12 to 65 years of age) with severe haemophilia A. Subjects on prophylaxis regimens prior to entering the study were assigned to the individualised prophylaxis arm. Subjects on on-demand therapy prior to entry either entered the individualised prophylaxis arm or were randomised to the weekly prophylaxis or on-demand arms.

Prophylaxis regimens:
Individualised prophylaxis: 25 to 65 IU/kg every 3 to 5 days. Weekly prophylaxis: 65 IU/kg

Out of 153 subjects who completed Study I, 150 were enrolled onto Study III (extension study). Median total time on Study I+III was 4.2 years and median number of exposure days was 309.

Individualised prophylaxis: Median annual factor consumption was 4212 IU/kg (min. 2877, max. 7943) in Study I and 4223 IU/kg (min. 2668, max 8317) in Study III. Respective median Annualized Bleed Rate (ABR) was 1.60 (min. 0, max. 18.2) and 0.74 (min. 0, max. 15.6).

Weekly prophylaxis: Median annual factor consumption was 3805 IU/kg (min. 3353, max. 6196) in Study I and 3510 IU/kg (min. 2758, max. 3984) in Study III. Respective median ABR was 3.59 (min. 0, max. 58.0) and 2.24 (min. 0, max. 17.2).

On-demand treatment: Median annual factor consumption was 1039 IU/kg (min. 280, max. 3571) for 23 patients randomised to the on-demand treatment arm in Study I and 671 IU/kg (min. 286, max. 913) for 6 patients remaining on on-demand treatment for at least one year in Study III.

Subjects that switched from on-demand treatment to weekly prophylaxis during Study III had a median ABR of 1.67.

Treatment of bleeding: 2490 bleeding events were treated during Study I and III with a median dose of 43.8 IU/kg (min. 13.0, max. 172.8) to control each bleed. 79.2 % of first injections were rated as excellent or good by the patients.

Perioperative management (surgical prophylaxis): A total of 48 major surgical procedures were performed and assessed in 34 subjects in Study I and Study III. The haemostatic response was rated by the physicians as excellent in 41 and as good in 3 of 44 major surgeries. Median dose to maintain haemostasis during surgery was 60.6 IU/kg (min. 38, max. 158).

Paediatric population

Study II enrolled a total of 71 previously treated male paediatric patients <12 years of age with severe haemophilia A. Of the 71 enrolled subjects, 69 received at least 1 dose of ELOCTA and were evaluable for efficacy (35 were <6 years of age and 34 were 6 to <12 years of age). The starting prophylactic regimen consisted of 25 IU/kg on the first day followed by 50 IU/kg on the fourth day. Dosing of up to 80 IU/kg and a dosing interval as short as 2 days was allowed and used in a limited number of patients. Out of 67 subjects having completed Study II, 61 enrolled onto Study III (extension study). Median total time on study II+III was 3.4 years and median number of exposure days was 332.

Prophylaxis, age <6 years: Median dose interval was 3.50 days in Study II and Study III. Median annual factor consumption was 5146 IU/kg (min. 3695, max 8474) in Study II and 5418 IU/kg (min. 3435, max. 9564) in Study III. Respective median Annualized Bleed Rate (ABR) was 0.00 (min. 0, max. 10.5) and 1.18 (min. 0, max. 9.2).

Prophylaxis, age 6 up to 12 years: Median dose interval was 3.49 days in Study II and 3.50 days in Study III. Median annual factor consumption was 4700 IU/kg (min. 3819, max. 8230 IU/kg) in Study II and 4990 IU/kg (min. 3856, max. 9527) in Study III. Respective median ABR was 2.01 (min. 0, max. 27.2) and 1.59 (min. 0, max. 8.0).

12 adolescent subjects age 12 up to 18 years were included in the adult study population on prophylactic treatment. Median annual factor consumption was 5572 IU/kg (min. 3849, max. 7035) in Study I and 4456 IU/kg (min. 3563, max. 8011) in Study III. Respective median ABR was 1.92 (min. 0, max. 7.1) and 1.25 (min. 0, max. 9.5).

Treatment of bleeding: During Studies II and III, 447 bleeding events were treated with a median dose of 63 IU/kg (min. 28, max. 186) to control each bleed. 90.2 % of first injections were rated as excellent or good by the patients and their caregivers.

Study IV evaluated 103male previously untreated patients (PUPs) <6 years of age with severe haemophilia A. Patients were followed for a total of 11,255 exposure days with a median of 100 (range 0-649) exposure days per patient. Most subjects started on episodic treatment (N=81) with subsequent transition to prophylaxis (N=69). At any time during the study, 89 PUPs received prophylaxis. The recommended initial dose on prophylaxis was 25–80 IU/kg at 3–5-day intervals. For subjects on prophylaxis, the median average weekly dose was 101.4 IU/kg (range: 28.5-776.3 IU/kg) and the median dosing interval was 3.87 days (range 1.1 to 7 days). Median annual factor consumption was 3971.4 IU/kg. Annualized Bleeding Rate was 1.49 (min. 0.0, max. 18.7).

5.2 Pharmacokinetic properties

All pharmacokinetic studies with ELOCTA were conducted in previously treated patients with severe haemophilia A. Data presented in this section were obtained by chromogenic and one-stage clotting assays. The pharmacokinetic parameters from the chromogenic assay data were similar to those derived for the one-stage assay.

Pharmacokinetic properties were evaluated in 28 subjects (≥15 years) receiving ELOCTA (rFVIIIFc). Following a washout period of at least 96 hours (4 days), the subjects received a single dose of 50 IU/kg of ELOCTA. Pharmacokinetic samples were collected pre-dose and then subsequently at 7 time points up to 120 hours (5 days) post-dose. Pharmacokinetic parameters after 50 IU/kg dose of ELOCTA are presented in Tables 3 and 4.

Table 3: Pharmacokinetic parameters of ELOCTA using the one-stage clotting assay

Pharmacokinetic parameters[1]	**ELOCTA (95% CI)**
	N=28
Incremental Recovery (IU/dL per IU/kg)	2.24 (2.11-2.38)
AUC/Dose (IU*h/dL per IU/kg)	51.2 (45.0-58.4)
C_{max} (IU/dL)	108 (101-115)
CL (mL/h/kg)	1.95 (1.71-2.22)
$t_{½}$ (h)	19.0 (17.0-21.1)
MRT (h)	25.2 (22.7-27.9)
V_{ss} (mL/kg)	49.1 (46.6-51.7)

[1] Pharmacokinetic parameters are presented in Geometric Mean (95% CI)

Abbreviations: CI = confidence interval; C_{max}= maximum activity; AUC = area under the FVIII activity time curve; $t_{½}$= terminal half-life; CL = clearance; V_{ss} = volume of distribution at steady-state; MRT = mean residence time.

Table 4: Pharmacokinetic parameters of ELOCTA using the chromogenic assay

Pharmacokinetic parameters[1]	**ELOCTA (95% CI)**
	N=27
Incremental Recovery (IU/dL per IU/kg)	2.49 (2.28-2.73)
AUC/Dose (IU*h/dL per IU/kg)	47.5 (41.6-54.2)
C_{max} (IU/dL)	131 (104-165)
CL (mL/h/kg)	2.11 (1.85-2.41)
$t_{½}$ (h)	20.9 (18.2-23.9)
MRT (h)	25.0 (22.4-27.8)
V_{ss} (mL/kg)	52.6 (47.4-58.3)

[1] Pharmacokinetic parameters are presented in Geometric Mean (95% CI)

Abbreviations: CI = confidence interval; C_{max}= maximum activity; AUC = area under the FVIII activity time curve; $t_{½}$= terminal half-life; CL = clearance; V_{ss} = volume of distribution at steady-state; MRT = mean residence time.

The PK data demonstrate that ELOCTA has a prolonged circulating half-life.

Paediatric population

Pharmacokinetic parameters of ELOCTA were determined for adolescents in study I (pharmacokinetic sampling was conducted pre-dose followed by assessment at multiple time points up to 120 hours (5 days) post-dose) and for children in study II (pharmacokinetic sampling was conducted pre-dose followed by assessment at multiple time points up to 72 hours (3 days) post-dose). Tables 5 and 6 present the pharmacokinetic parameters calculated from the paediatric data of subjects less than 18 years of age.

Table 5: Pharmacokinetic parameters of ELOCTA for paediatrics using the one-stage clotting assay

Pharmacokinetic parameters[1]	**Study II**			**Study I***
	<6 years	**6 to <12 years**		**12 to <18 years**
	N = 23	N = 31		N = 11
Incremental Recovery (IU/dL per IU/kg)	1.90 (1.79-2.02)	2.30 (2.04-2.59)		1.81 (1.56-2.09)
AUC/Dose (IU*h/dL per IU/kg)	28.9 (25.6-32.7)	38.4 (33.2-44.4)		38.2 (34.0-42.9)
$t_{½}$ (h)	12.3 (11.0-13.7)	13.5 (11.4-15.8)		16.0 (13.9-18.5)
MRT (h)	16.8 (15.1-18.6)	19.0 (16.2-22.3)		22.7 (19.7-26.1)
CL (mL/h/kg)	3.46 (3.06-3.91)	2.61 (2.26-3.01)		2.62 (2.33-2.95)
V_{ss} (mL/kg)	57.9 (54.1-62.0)	49.5 (44.1-55.6)		59.4 (52.7-67.0)

[1] Pharmacokinetic parameters are presented in Geometric Mean (95% CI)
Abbreviations: CI = confidence interval; AUC = area under the FVIII activity time curve; $t_{½}$ = terminal half-life;
CL = clearance; MRT = mean residence time; V_{ss} = volume of distribution at steady-state
*Pharmacokinetic parameters in 12 to <18 years included subjects from all the arms in Study I with different sampling schemes

Table 6: Pharmacokinetic parameters of ELOCTA for paediatrics using the chromogenic assay

Pharmacokinetic parameters[1]	Study II			Study I*
	<6 years	6 to <12 years		12 to <18 years
	N = 24	N = 27		N = 11
Incremental Recovery (IU/dL per IU/kg)	1.88 (1.73-2.05)	2.08 (1.91-2.25)		1.91 (1.61-2.27)
AUC/Dose (IU*h/dL per IU/kg)	25.9 (23.4-28.7)	32.8 (28.2-38.2)		40.8 (29.3-56.7)
$t_{½}$ (h)	14.3 (12.6-16.2)	15.9 (13.8-18.2)		17.5 (12.7-24.0)
MRT (h)	17.2 (15.4-19.3)	20.7 (18.0-23.8)		23.5 (17.0-32.4)
CL (mL/h/kg)	3.86 (3.48-4.28)	3.05 (2.62-3.55)		2.45 (1.76-3.41)
V_{ss} (mL/kg)	66.5 (59.8-73.9)	63.1 (56.3-70.9)		57.6 (50.2-65.9)

[1] Pharmacokinetic parameters are presented in Geometric Mean (95% CI)
Abbreviations: CI = confidence interval; AUC = area under the FVIII activity time curve; $t_{½}$ = terminal half-life;
CL = clearance; MRT = mean residence time; V_{ss} = volume of distribution at steady-state
* Pharmacokinetic parameters in 12 to <18 years included subjects from all the arms in Study I with different sampling schemes

In comparison with adolescents and adults, children less than 12 years of age may have a higher clearance and a shorter half-life which is consistent with observations of other coagulation factors. These differences should be taken into account when dosing.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on acute and repeated dose toxicity studies (which included assessments of local toxicity and safety pharmacology). Studies to investigate genotoxicity, carcinogenicity, toxicity to reproduction or embryo-foetal development have not been conducted. In a placental transfer study, ELOCTA has been shown to cross the placenta in small amounts in mice.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

Sucrose

Sodium chloride

Histidine

Calcium chloride dihydrate

Polysorbate 20

Sodium hydroxide (for pH adjustment)

Hydrochloric acid (for pH adjustment)

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

6.3 Shelf life

Unopened vial 5 years

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 expiry date printed on the vial or six months after removing the carton from refrigeration, whichever is earlier.

After reconstitution

After reconstitution, chemical and physical stability has been demonstrated for 6 hours when stored at room temperature (up to 30°C). Protect product from direct sunlight. After reconstitution, if the product is not used within 6 hours, it must be discarded. From a microbiological point of view, 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.

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 contains:

- powder in a type 1 glass vial with a chlorobutyl rubber stopper
- 3 mL solvent in a type 1 glass pre-filled syringe with a bromobutyl rubber plunger stopper
- a plunger rod
- a sterile vial adapter for reconstitution
- a sterile infusion set
- two alcohol swabs
- two plasters
- one gauze pad.

Pack size of 1.

6.6 Special precautions for disposal

The vial of lyophilised product powder for injection must be

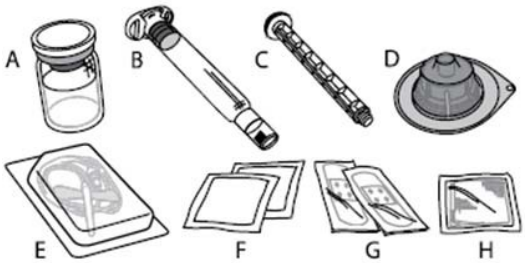
reconstituted with the supplied solvent (water for injections) from the pre-filled syringe using the sterile vial adapter for reconstitution.

The vial should be gently swirled until all of the powder is dissolved.

Reconstituted medicinal product should be inspected visually for particulate matter and discoloration prior to administration. The solution should be clear to slightly opalescent and colourless. Do not use solutions that are cloudy or have deposits.

Additional information on reconstitution and administration:

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



A) 1 Powder vial
B) 3 mL solvent in pre-filled syringe
C) 1 Plunger rod
D) 1 Vial adapter
E) 1 Infusion set
F) 2 Alcohol swabs
G) 2 Plasters
H) 1 Gauze pad

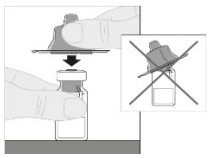
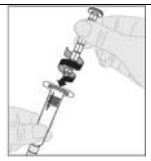
ELOCTA should not be mixed with other solutions for

injection or infusion. Wash your hands before opening the

pack

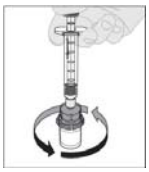
Preparation:

1. Check the name and strength of the package, to make sure it contains the correct medicine. Check the expiry date on the ELOCTA carton. Do not use if the medicine has expired.
2. If ELOCTA has been stored in a refrigerator, allow the vial of ELOCTA (A) and the syringe with solvent (B) to reach room temperature before use. Do not use external heat.

3. Place the vial on a clean flat surface. Remove the plastic flip-top cap from the ELOCTA vial.	
4. Wipe the top of the vial with one of the alcohol swabs (F) provided in the pack, and allow to air dry. Do not touch the top of the vial or allow it to touch anything else once wiped.	
5. Peel back the protective paper lid from the clear plastic vial adapter (D). Do not remove the adapter from its protective cap. Do not touch the inside of the vial adapter package.	
6. Place the vial on a flat surface. Hold the vial adapter in its protective cap and place it squarely over the top of the vial. Press down firmly until the adapter snaps into place on top of the vial, with the adapter spike penetrating the vial stopper.	
7. Attach the plunger rod (C) to the solvent syringe by inserting the tip of the plunger rod into the opening in the syringe plunger. Turn the plunger rod firmly clockwise until it is securely seated in the syringe plunger.	
8. Break off the white, tamper-resistant, plastic cap from the solvent syringe by bending at the perforation cap until it snaps off. Set the cap aside by placing it with the top down on a flat surface. Do not touch the inside of the cap or the syringe tip.	
9. Lift the protective cap away from the adapter and discard.	
10. Connect the solvent syringe to the vial adapter by inserting the tip of the syringe into the adapter opening. Firmly push and turn the syringe clockwise until it is securely connected.	

11. Slowly depress the plunger rod to inject all the solvent into the ELOCTA vial.

12. With the syringe still connected to the adapter and the plunger rod pressed down, gently swirl the vial until the powder is dissolved.
Do not shake.



13. The final solution must be inspected visually before administration. The solution should appear clear to slightly opalescent and colourless. Do not use the solution if cloudy or contains visible particles.

14. Ensuring that the syringe plunger rod is still fully pressed down, invert the vial. Slowly pull on the plunger rod to draw back all the solution through the vial adapter into the syringe.

15. Detach the syringe from the vial adapter by gently pulling and turning the vial counterclockwise.

Note: If you use more than one vial of ELOCTA per injection, each vial should be prepared separately as per the previous instructions (steps 1 to 13) and the solvent syringe should be removed, leaving the vial adapter in place. A single large luer lock syringe may be used to draw back the prepared contents of each of the individual vials.

16. Discard the vial and the adapter.

Note: If the solution is not to be used immediately, the syringe cap should be carefully put back on the syringe tip. Do not touch the syringe tip or the inside of the cap.

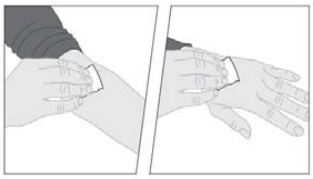
After preparation, ELOCTA can be stored at room temperature for up to 6 hours before administration. After this time, the prepared ELOCTA should be discarded. Protect from direct sunlight.

Administration (Intravenous injection):

ELOCTA should be administered using the infusion set (E) provided in this pack.

1. Open the infusion set package and remove the cap at the end of the tubing. Attach the syringe with the prepared ELOCTA solution to the end of the infusion set tubing by turning clockwise.

2. If needed apply a tourniquet and prepare the injection site by wiping the skin well with the other alcohol swab provided in the pack.



3. Remove any air in the infusion set tubing by slowly depressing on the plunger rod until liquid has reached the infusion set needle. Do not push the solution through the needle. Remove the clear plastic protective cover from the needle.

4. Insert the infusion set needle into a vein as instructed by your doctor or nurse and remove the tourniquet. If preferred, you may use one of the plasters (G) provided in the pack to hold the plastic wings of the needle in place at the injection site. The prepared product should be injected intravenously over several minutes. Your doctor may change your recommended injection rate to make it more comfortable for you.

5. After completing the injection and removing the needle, you should fold over the needle protector and snap it over the needle.

6. Please safely dispose of the used needle, any unused solution, the syringe and the empty vial in an appropriate medical waste container as these materials may hurt others if not disposed of properly. Do not reuse equipment.

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

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