ANNEX I

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

ELOCTA 250 IU powder and solvent for solution for injection

ELOCTA 500 IU powder and solvent for solution for injection

ELOCTA 750 IU powder and solvent for solution for injection

ELOCTA 1000 IU powder and solvent for solution for injection

ELOCTA 1500 IU powder and solvent for solution for injection

ELOCTA 2000 IU powder and solvent for solution for injection

ELOCTA 3000 IU powder and solvent for solution for injection

ELOCTA 4000 IU powder and solvent for solution for injection

ELOCTA 5000 IU powder and solvent for solution for injection

ELOCTA 6000 IU powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ELOCTA 250 IU powder and solvent for solution for injection
Each vial contains nominally 250 IU efmoroctocog alfa. After reconstitution, each mL of solution for injection contains approximately 83 IU efmoroctocog alfa.

ELOCTA 500 IU powder and solvent for solution for injection
Each vial contains nominally 500 IU efmoroctocog alfa. After reconstitution, each mL of solution for injection contains approximately 167 IU efmoroctocog alfa.

ELOCTA 750 IU powder and solvent for solution for injection
Each vial contains nominally 750 IU efmoroctocog alfa. After reconstitution, each mL of solution for injection contains approximately 250 IU efmoroctocog alfa.

ELOCTA 1000 IU powder and solvent for solution for injection
Each vial contains nominally 1000 IU efmoroctocog alfa. After reconstitution, each mL of solution for injection contains approximately 333 IU efmoroctocog alfa.

ELOCTA 1500 IU powder and solvent for solution for injection
Each vial contains nominally 1500 IU efmoroctocog alfa. After reconstitution, each mL of solution for injection contains approximately 500 IU efmoroctocog alfa.

ELOCTA 2000 IU powder and solvent for solution for injection
Each vial contains nominally 2000 IU efmoroctocog alfa. After reconstitution, each mL of solution for injection contains approximately 667 IU efmoroctocog alfa.

ELOCTA 3000 IU powder and solvent for solution for injection
Each vial contains nominally 3000 IU efmoroctocog alfa. After reconstitution, each mL of solution for injection contains approximately 1000 IU efmoroctocog alfa.

ELOCTA 4000 IU powder and solvent for solution for injection
Each vial contains nominally 4000 IU efmoroctocog alfa. After reconstitution, each mL of solution for injection contains approximately 1333 IU efmoroctocog alfa.

ELOCTA 5000 IU powder and solvent for solution for injection
Each vial contains nominally 5000 IU efmoroctocog alfa. After reconstitution, each mL of solution for injection contains approximately 1667 IU efmoroctocog alfa.

ELOCTA 6000 IU powder and solvent for solution for injection
Each vial contains nominally 6000 IU efmoroctocog alfa. After reconstitution, each mL of solution for injection contains approximately 2000 IU efmoroctocog alfa.

The potency (International Units) is determined using the European Pharmacopoeia chromogenic assay against an in-house standard that is referenced to the WHO factor VIII standard. 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.

Previously untreated patients
The safety and efficacy of ELOCTA in previously untreated patients have not yet been established. No data are available.

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 recombinant factor VIII Fc administered is expressed in International Units (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 International Units (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 International Unit (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) x desired factor VIII rise (%) (IU/dL) x 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 (see section 5.2). The time to peak activity is not expected to be delayed.

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/kg every 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.

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. This is of importance particularly when changing the laboratory and/or reagent used in the assay.

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 (recombinant human coagulation factor VIII, and/or Fc domain) 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 anaphylactic 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 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days.

Cases of recurrent inhibitor (low titre) have been observed after switching from one factor VIII product to another in previously treated patients with more than 100 exposure days who have a previous history of inhibitor development. Therefore, it is recommended to monitor all patients carefully for inhibitor occurrence following any product switch.

The clinical relevance of inhibitor development will depend on the titre of the inhibitor, with low titre inhibitors which are transiently present or remain consistently 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.

Recording of batch number
It is strongly recommended that every time that ELOCTA is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the medicinal product.

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'.

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

Pregnancy and breast-feeding
Animal reproduction studies have not been conducted with ELOCTA. A placental transfer study in mice was conducted (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.

Fertility
There are no fertility data available. No fertility studies have been conducted in animals with ELOCTA.

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 swelling of the face, rash, hives, tightness of the chest and difficulty breathing, burning and stinging at the infusion site, chills, flushing, generalised urticaria, headache, hypotension, lethargy, nausea, restlessness, tachycardia) 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 frequencies in Table 2 below were observed in a total of 276 patients with severe haemophilia A in phase III clinical studies and an extension study with a duration of up to four years. Adverse reactions were monitored for a total of 893.72 subject-years. The total number of exposure days was 80,848 with a median of 294 (range 1-735) exposure days per subject.

The Table 2 presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level).

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

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

[1] Frequency is based on studies with all FVIII products which included patients with severe haemophilia A. PTPs= previously treated patients.

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

Paediatric population

No age-specific differences in adverse reactions were observed between paediatric and adult subjects.

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 national reporting system listed in Appendix V.

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 2 molecules (factor VIII and von Willebrand factor) with different physiological functions. Upon activation of the clotting cascade, factor VIII is converted to activated factor VIII and released from von Willebrand factor. Activated factor VIII acts as a cofactor for activated factor IX, accelerating the conversion of factor X to activated factor X on phospholipid surfaces. 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 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.

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 were evaluated in 2 multinational, open-label, pivotal studies; a phase 3 study, referred to as Study I and a phase 3 paediatric study, referred to as Study II (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 no 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.

Of note, ABR is not comparable between different factor concentrates and between different clinical studies.

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 no 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: 447 bleeding events were treated during Study II and III 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.

Immunogenicity
The immunogenicity of ELOCTA was evaluated in the clinical trial programme in 276 previously treated patients with severe haemophilia A (207 adolescents and adult and 69 paediatric patients). None of these patients developed inhibitors.

The European Medicines Agency has deferred the obligation to submit the results of studies with ELOCTA in one or more subsets of the paediatric population in the treatment of hereditary Factor VIII deficiency (see section 4.2 for information on paediatric use).

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
L-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
4 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 and other handling

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.

See package leaflet for additional information on reconstitution and administration.

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

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

7. MARKETING AUTHORISATION HOLDER

Swedish Orphan Biovitrum AB (publ)
SE-112 76 Stockholm
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1046/001
EU/1/15/1046/002
EU/1/15/1046/003
EU/1/15/1046/004
EU/1/15/1046/005
EU/1/15/1046/006
EU/1/15/1046/007
EU/1/15/1046/008
EU/1/15/1046/009
EU/1/15/1046/010

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 November 2015

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substance

Biogen Inc
250 Binney Street
Cambridge, MA
02142
USA

Biogen Inc.
5000 Davis Drive
Research Triangle Park, NC 27709
USA

Name and address of the manufacturer responsible for batch release

Swedish Orphan Biovitrum AB (publ)
Strandbergsgatan 49
SE-112 76 Stockholm
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B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

ELOCTA 250 IU powder and solvent for solution for injection

ELOCTA 500 IU powder and solvent for solution for injection

ELOCTA 750 IU powder and solvent for solution for injection

ELOCTA 1000 IU powder and solvent for solution for injection

ELOCTA 1500 IU powder and solvent for solution for injection

ELOCTA 2000 IU powder and solvent for solution for injection

ELOCTA 3000 IU powder and solvent for solution for injection

ELOCTA 4000 IU powder and solvent for solution for injection

ELOCTA 5000 IU powder and solvent for solution for injection

ELOCTA 6000 IU powder and solvent for solution for injection

efmoroctocog alfa
recombinant coagulation factor VIII, Fc fusion protein

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Powder: 250 IU efmoroctocog alfa (approx. 83 IU/mL after reconstitution)

Powder: 500 IU efmoroctocog alfa (approx. 167 IU/mL after reconstitution)

Powder: 750 IU efmoroctocog alfa (approx. 250 IU/mL after reconstitution)

Powder: 1000 IU efmoroctocog alfa (approx. 333 IU/mL after reconstitution)

Powder: 1500 IU efmoroctocog alfa (approx. 500 IU/mL after reconstitution)

Powder: 2000 IU efmoroctocog alfa (approx. 667 IU/mL after reconstitution)

Powder: 3000 IU efmoroctocog alfa (approx. 1000 IU/mL after reconstitution)

Powder: 4000 IU efmoroctocog alfa (approx. 1333 IU/mL after reconstitution)

Powder: 5000 IU efmoroctocog alfa (approx. 1667 IU/mL after reconstitution)

Powder: 6000 IU efmoroctocog alfa (approx. 2000 IU/mL after reconstitution)

3. LIST OF EXCIPIENTS

Powder: sucrose, sodium chloride, L-Histidine, calcium chloride dihydrate, polysorbate 20, sodium hydroxide, hydrochloric acid.

Solvent: water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection

Content: 1 powder vial, 3 mL solvent in pre-filled syringe, 1 plunger rod, 1 vial adapter, 1 infusion set, 2 alcohol swabs, 2 plasters, 1 gauze.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intravenous use, after reconstitution.
Read the package leaflet before use.

An instructional video on how to prepare and administer ELOCTA is available by scanning the QR code with a smartphone or via the website.

QR code to be included+ http://www.elocta-instructions.com

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

Use within 6 hours after reconstitution.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.
Can be stored at room temperature (up to 30°C) for a single period up to 6 months. Must not be returned to refrigerator after storage at room temperature. Date removed from refrigerator:

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Swedish Orphan Biovitrum AB (publ)
SE-112 76 Stockholm
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/15/1046/001
EU/1/15/1046/002
EU/1/15/1046/003
EU/1/15/1046/004
EU/1/15/1046/005
EU/1/15/1046/006
EU/1/15/1046/007
EU/1/15/1046/008
EU/1/15/1046/009
EU/1/15/1046/010

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

ELOCTA 250

ELOCTA 500

ELOCTA 750

ELOCTA 1000

ELOCTA 1500

ELOCTA 2000

ELOCTA 3000

ELOCTA 4000

ELOCTA 5000

ELOCTA 6000

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ELOCTA 250 IU powder for injection

ELOCTA 500 IU powder for injection

ELOCTA 750 IU powder for injection

ELOCTA 1000 IU powder for injection

ELOCTA 1500 IU powder for injection

ELOCTA 2000 IU powder for injection

ELOCTA 3000 IU powder for injection

ELOCTA 4000 IU powder for injection

ELOCTA 5000 IU powder for injection

ELOCTA 6000 IU powder for injection

efmoroctocog alfa
recombinant coagulation factor VIII
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

250 IU

500 IU

750 IU

1000 IU

1500 IU

2000 IU

3000 IU

4000 IU

5000 IU

6000 IU

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Solvent for ELOCTA
water for injections

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: information for the user

ELOCTA 250 IU powder and solvent for solution for injection
ELOCTA 500 IU powder and solvent for solution for injection
ELOCTA 750 IU powder and solvent for solution for injection
ELOCTA 1000 IU powder and solvent for solution for injection
ELOCTA 1500 IU powder and solvent for solution for injection
ELOCTA 2000 IU powder and solvent for solution for injection
ELOCTA 3000 IU powder and solvent for solution for injection
ELOCTA 4000 IU powder and solvent for solution for injection
ELOCTA 5000 IU powder and solvent for solution for injection
ELOCTA 6000 IU powder and solvent for solution for injection

efmoroctocog alfa (recombinant coagulation factor VIII)

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What ELOCTA is and what it is used for

ELOCTA contains the active substance efmoroctocog alfa, a recombinant coagulation factor VIII, Fc fusion protein. Factor VIII is a protein produced naturally in the body and is necessary for the blood to form clots and stop bleeding.
ELOCTA is a medicine used for the treatment and prevention of bleeding in all age groups of patients with haemophilia A (inherited bleeding disorder caused by factor VIII deficiency).

ELOCTA is prepared by recombinant technology without addition of any human- or animal-derived components in the manufacturing process.

How ELOCTA works
In patients with haemophilia A, factor VIII is missing or not working properly. ELOCTA is used to replace the missing or deficient factor VIII. ELOCTA increases factor VIII level in the blood and temporarily corrects the bleeding tendency.

2. What you need to know before you use ELOCTA

Do not use ELOCTA:
- if you are allergic to efmoroctocog alfa or any other ingredients of this medicine (listed in section 6).

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using ELOCTA.

- There is a small chance that you may experience an anaphylactic reaction (a severe, sudden allergic reaction) to ELOCTA. Signs of allergic reactions may include generalised itching, hives, tightness of the chest, difficulty breathing and low blood pressure. If any of these symptoms occur, stop the injection immediately and contact your doctor.

- The formation of inhibitors (antibodies) is a known complication that can occur during treatment with all factor VIII medicines. These inhibitors, especially at high levels, stop the treatment working properly and you or your child will be monitored carefully for the development of these inhibitors. If your or your child's bleeding is not being controlled with ELOCTA, tell your doctor immediately.

Catheter-related complications
If you require a central venous access device (CVAD), risk of CVAD-related complications including local infections, presence of bacteria in the blood and catheter site thrombosis should be considered.

Documentation
It is strongly recommended that every time ELOCTA is given, the name and batch number of the product are recorded.

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

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Driving and using machines
No effects on ability to drive or use of machines have been observed.

ELOCTA contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium-free'.

3. How to use ELOCTA

Treatment with ELOCTA will be started by a doctor who is experienced in the care of patients with haemophilia. Always use this medicine exactly as your doctor has told you (see section 7). Check with your doctor, pharmacist or nurse if you are not sure.

ELOCTA is given as an injection into a vein. Your doctor will calculate your dose of ELOCTA (in International Units or "IU") depending on your individual needs for factor VIII replacement therapy and on whether it is used for prevention or treatment of bleeding. Talk to your doctor if you think that your bleeding is not being controlled with the dose you receive.

How often you need an injection will depend on how well ELOCTA is working for you. Your doctor will perform appropriate laboratory tests to make sure that you have adequate factor VIII levels in your blood.

Treatment of bleeding
The dose of ELOCTA is calculated depending on your body weight and the factor VIII levels to be achieved. The target factor VIII levels will depend on the severity and location of the bleeding.

Prevention of bleeding
The usual dose of ELOCTA is 50 IU per kg of body weight, given every 3 to 5 days. The dose may be adjusted by your doctor in the range of 25 to 65 IU per kg of body weight. In some cases, especially in younger patients, shorter dosing intervals or higher doses may be necessary.

Use in children and adolescents
ELOCTA can be used in children and adolescents of all ages. In children below the age of 12, higher doses or more frequent injections may be needed.

If you use more ELOCTA than you should
Tell your doctor as soon as possible. You should always use ELOCTA exactly as your doctor has told you, check with your doctor, pharmacist or nurse if you are not sure.

If you forget to use ELOCTA
Do not take a double dose to make up for a forgotten dose. Take your dose as soon as you remember and then resume your normal dosing schedule. If you are not sure what to do, ask your doctor or pharmacist.

If you stop using ELOCTA
Do not stop using ELOCTA without consulting your doctor. If you stop using ELOCTA you may no longer be protected against bleeding or a current bleed may not stop.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

If severe, sudden allergic reactions (anaphylactic reaction) occur, the injection must be stopped immediately. You must contact your doctor immediately if you experience any of the following symptoms of allergic reactions: swelling of the face, rash, generalised itching, hives, tightness of the chest, difficulty breathing**,** burning and stinging at the injection site, chills, flushing, headache, low blood pressure, general feeling of being unwell, nausea, restlessness and fast heartbeat, feeling dizzy or loss of consciousness.

For patients who have received previous treatment with factor VIII (more than 150 days of treatment) inhibitor antibodies (see section 2) may form uncommonly (less than 1 in 100 patients). If this happens your medicine may stop working properly and you may experience persistent bleeding. If this happens, you should contact your doctor immediately.

The following side effects may occur with this medicine.

Uncommon side effects (may affect up to 1 in 100 people)
Headache, dizziness, taste alteration, slow heartbeat, high blood pressure, hot flushes, vascular pain after injection, cough, abdominal pain, rash, joint swelling, muscle pain, back pain, joint pain, general discomfort, chest pain, feeling cold, feeling hot and low blood pressure.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store ELOCTA

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the vial label after “EXP”. The expiry date refers to the last day of that month. Do not use this medicine if it has been stored at room temperature for longer than 6 months.

Store in a refrigerator (2°C - 8°C).
Do not freeze.
Store in the original package in order to protect from light.

Alternatively, ELOCTA may be stored at room temperature (up to 30°C) for a single period not exceeding 6 months. Record on the carton the date that ELOCTA is removed from the refrigerator and set at room temperature. After storage at room temperature, the product must not be put back in the refrigerator.

Once you have prepared ELOCTA it should be used right away. If you cannot use the prepared ELOCTA solution immediately, it should be used within 6 hours. Do not refrigerate the prepared solution. Protect the prepared solution from direct sunlight.

The prepared solution will be clear to slightly opalescent and colourless. Do not use this medicine if you notice that it is cloudy or contains visible particles.

Discard any unused solution appropriately. Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What ELOCTA contains

- The active substance is efmoroctocog alfa (recombinant coagulation factor VIII, Fc fusion protein). Each vial of ELOCTA contains nominally 250, 500, 750, 1000, 1500, 2000, 3000, 4000, 5000 or 6000 IU efmoroctocog alfa.
- The other ingredients are sucrose, sodium chloride, L-Histidine, calcium chloride dihydrate, polysorbate 20, sodium hydroxide, hydrochloric acid and water for injections. If you are on a controlled sodium diet see section 2.

What ELOCTA looks like and contents of the pack

ELOCTA is provided as a powder and solvent for solution for injection. The powder is a white to off-white powder or cake. The solvent provided for preparation of the solution to inject, is a clear, colourless solution. After preparation, the solution to inject is clear to slightly opalescent and colourless.

Each pack of ELOCTA contains 1 powder vial, 3 mL solvent in pre-filled syringe, 1 plunger rod, 1vial adapter, 1 infusion set, 2 alcohol swabs, 2 plasters and 1 gauze pad.

Marketing Authorisation Holder and Manufacturer
Swedish Orphan Biovitrum AB (publ)
SE-112 76 Stockholm,
Sweden

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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e-mail: mail.uk@sobi.com

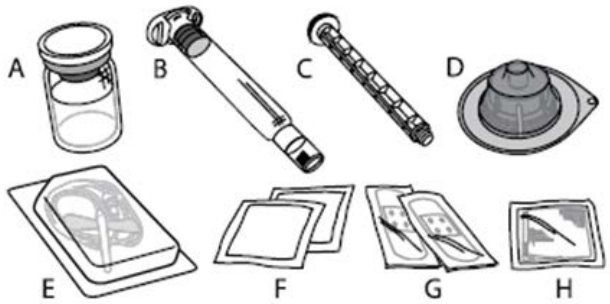
This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: **Error! Hyperlink reference not valid.**.

Turn the leaflet over for section 7. Instructions for preparation and administration

7. Instructions for preparation 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:

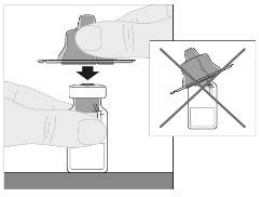


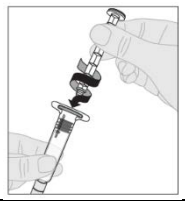
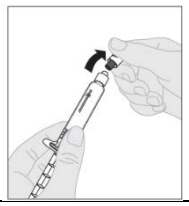
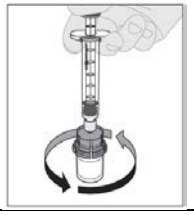
A) 1 Powder vial
B) 3 mL solvent in pre-filled syringe
C) 1 Plunger rod
D) 1 Vial adapter
E) 1 Infusion set
F) 2 Alcohol swabs
G) 2 Plasters
H) 1 Gauze pad

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.	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.

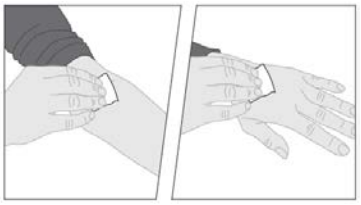
After preparation, ELOCTA can be stored at room temperature for up to 6 hours before administration. After this time, the prepared ELOCTA should be discarded. Protect from direct sunlight.

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.

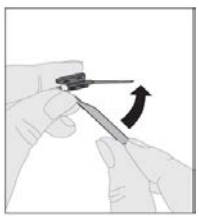
2. If needed apply a tourniquet and prepare the injection site by wiping the skin well with the other alcohol swab provided in the pack.



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.