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

CEVENFACTA 1 mg (45 KIU) powder and solvent for solution for injection
CEVENFACTA 2 mg (90 KIU) powder and solvent for solution for injection
CEVENFACTA 5 mg (225 KIU) powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

CEVENFACTA 1 mg (45 KIU) powder and solvent for solution for injection

Each vial contains nominally 1 mg eptacog beta (activated) (45 KIU/vial) corresponding to a concentration of approximately 1 mg/mL (45 KIU/mL) when reconstituted with 1.1 mL of water for injections.

CEVENFACTA 2 mg (90 KIU) powder and solvent for solution for injection

Each vial contains nominally 2 mg eptacog beta (activated) (90 KIU/vial) corresponding to a concentration of approximately 1 mg/mL (45 KIU/mL) when reconstituted with 2.2 mL of water for injections.

CEVENFACTA 5 mg (225 KIU) powder and solvent for solution for injection

Each vial contains nominally 5 mg eptacog beta (activated)(225 KIU/vial) corresponding to a concentration of approximately 1 mg/mL (45 KIU/mL) when reconstituted with 5.2 mL of water for injections.

The potency (IU) is determined using a clotting assay. 1 KIU equals 1 000 IU (International Units).

Eptacog beta (activated) is a recombinant coagulation Factor VIIa (rFVIIa) with a molecular mass of approximately 50 000 Daltons produced from rabbit milk by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

White to off-white lyophilised powder.
Solvent: clear and colourless solution.

The solution has a pH of approximately 6. The osmolality is approximately 290 mOsm/kg.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CEVENFACTA is indicated in adults and adolescents (12 years of age and older) for the treatment of bleeding episodes and for the prevention of bleeding in those undergoing surgery or invasive procedures in the following patient groups:

- in patients with congenital haemophilia with high-responding inhibitors to coagulation factors VIII or IX (i.e. ≥5 Bethesda Units (BU));
- in patients with congenital haemophilia with low titre inhibitors (BU <5), but expected to have a high anamnestic response to factor VIII or factor IX administration or expected to be refractory to increased dosing of FVIII or FIX.

4.2 Posology and method of administration

Treatment should be initiated and supervised by a physician experienced in the treatment of haemophilia and/or bleeding disorders.

Posology

The dose and duration of treatment depend on the location and severity of the bleeding or the type of surgery/procedure, the need for urgent haemostasis, the frequency of administration, and the known patient responsiveness to FVIIa-containing bypassing agents during prior bleeding events.

The results of laboratory assessment(s) of coagulation (prothrombin time (PT)/international normalised ratio (INR), activated partial thromboplastin time (aPTT), FVII coagulation activity (Clotting time) (FVII:C)) do not necessarily correlate with or predict the haemostatic effectiveness of this medicinal product.

The dose, frequency, and duration of CEVENFACTA therapy should be based on the patient's clinical response and haemostasis evaluation.

Maximum tolerated doses have not been determined for this medicinal product and cumulative daily doses greater than 1 025 µg/kg have not been studied.

Treatment of bleeding episodes
Treatment with this medicinal product should be initiated as soon as a bleeding event occurs.

The recommended initial dose should be adjusted based on the criteria provided in Table 1.

For mild to moderate bleeding episodes, the duration of home therapy should not exceed 24 hours. Only after consultation with the haemophilia treatment centre can continued home treatment be considered.

If signs or symptoms of severe bleeding occur in the home setting, immediate medical care should be sought by patients. In the meantime, to avoid any treatment delay, an initial dose can be administered at home.

In all situations, if an adequate haemostatic response is not achieved (e.g., within 24 hours of the first administration of CEVENFACTA for mild and moderate bleeding episodes), alternative therapies should be considered.

Table 1: Dosing for the treatment of bleeding episodes

Type of bleeding	Dosing regimen recommendation	Duration of therapy
Mild and moderate Joint, superficial muscle, soft	75 µg/kg repeated every 3 hours until haemostasis is achieved. or	Continue therapy to support healing and prevent recurrent haemorrhage after

tissue, and mucous membranes.	Initial dose of 225 µg/kg. If haemostasis is not achieved within 9 hours, additional 75 µg/kg doses may be administered every 3 hours as needed to achieve haemostasis. The following factors should be considered when choosing the initial dose of this medicinal product: • The severity and site of bleeding and need for urgent haemostasis • Frequency of administration • Known patient responsiveness to FVIIa-containing bypassing agents during prior bleeding events	haemostasis to maintain the haemostatic plug. The site and severity of bleeding should determine therapy duration.
Severe Life or limb threatening haemorrhage, iliopsoas and deep muscle with neurovascular injury, retroperitoneum, intracranial, or gastrointestinal.	225 µg/kg initially, followed if necessary 6 hours later with 75 µg/kg every 2 hours until haemostasis is achieved. Subsequent dosing: After achieving haemostasis, the decision for dosing should be based on the clinical assessment and the type of bleeding bearing in mind relevant warning and precautions (see section 4.4).	Continue therapy to support healing and prevent recurrent haemorrhage. The site and severity of bleeding and the use of other procoagulant therapies should determine therapy duration.

There was limited experience with severe bleedings in the PerSept 1 clinical study.

Prevention of bleeding during surgical or invasive procedures
CEVENFACTA dosing for the prevention of bleeding during surgical or invasive procedures (perioperative management) is provided in Table 2.

Table 2: Dosing for perioperative management of bleeding

Type of surgical procedure	Dosing regimen recommendation	Duration of therapy
Minor Including uncomplicated tooth extraction, peripheral central catheter insertion, Port-a-Cath placement, etc.	**Initial dose**: 75 µg/kg immediately before surgery or start of invasive procedure; then **Subsequent doses**: 75 µg/kg repeated every 2 hours for the first 48 hours following the initial dose.	Most minor procedures should be treated for 48 hours to achieve haemostasis. At the discretion of the clinician, this medicinal product may be administered less frequently than every 2 hours and/or for less than 48 hours.
Major	**Pre-operative and operative doses**: 200 µg/kg immediately before the surgery, followed by 75 µg/kg every 2 hours for the duration of the surgery	This medicinal product should be administered for a minimum of 5 postoperative days (120 hours) and for as long as necessary to achieve

	The following post-operative doses may be administered: • First 48 hours: 75 µg/kg every 2 hours • Days 3-4: 75 µg/kg every 2 to 4 hours • Days 5-6: 75 µg/kg every 2 to 6 hours • Days 7-10: 75 µg/kg every 2 to 8 hours • Day 11 onwards: 75 µg/kg every 2 to 12 hours The dose and dosing intervals may be adjusted by the healthcare provider based on the clinical assessment and known patient responsiveness to FVIIa-containing bypassing agents. Following the surgery, CEVENFACTA (75 µg/kg) is also recommended prior to drain or suture removal or physical therapy.	haemostasis and support wound healing.

Close follow-up is important for early detection of potential postoperative bleeding events that may require adjustment of the dosing intervals.

Special population

The dosing regimen in elderly patients and in patients with renal or hepatic impairment has not yet been established (see sections 4.4 and 5.2).

Paediatric population

The efficacy of CEVENFACTA in children <12 years has not been established. Currently available data are described in sections 4.8 and 5.1 but no recommendation on a posology can be made.

In line with the European Medicines Agency recommendations, there is no relevant use of CEVENFACTA for the treatment of congenital haemophilia in the paediatric population from birth to less than 6 months.

Method of administration

For instructions on reconstitution of the medicinal product before administration, see section 6.6. Administer the solution as an intravenous bolus injection over 2 minutes or less.

4.3 Contraindications

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

4.4 Special warnings and precautions for use

Traceability

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

Thrombosis

There is limited information about the safety of this medicinal product in patients with a history of arterial or venous thromboembolic disease, because such patients were excluded from CEVENFACTA clinical studies. Such reactions have been reported in clinical studies and post-marketing surveillance with eptacog alfa and aPCC/PCC (activated or non-activated prothrombin complex).

The following patients may be at an increased risk of thromboembolic events with use of this medicinal product:

- History of congenital or acquired haemophilia receiving concomitant treatment with aPCC/PCC or other haemostatic agents (see section 4.5);
- History of atherosclerosis, coronary artery disease, cerebrovascular disease, crush injury, septicaemia, or thromboembolism.

Patients receiving this medicinal product should be monitored for the development of signs and symptoms of activation of the coagulation system or thrombosis. When there is laboratory confirmation of intravascular coagulation or presence of clinical thrombosis, the dose of this medicinal product should be reduced or treatment should be stopped, depending on the patient's condition.

Hypersensitivity reactions

Hypersensitivity reactions, including anaphylaxis, may occur with this medicinal product. Symptoms may include hives, itching, rash, difficulty breathing, swelling around the mouth and throat, tightness of the chest, wheezing, dizziness or fainting, and low blood pressure. In the event of hypersensitivity reactions, patients should discontinue treatment and seek immediate medical attention.

Patients with known IgE-based hypersensitivity to casein may be at a higher risk of hypersensitivity reactions. Should signs or symptoms of hypersensitivity occur, treatment should be discontinued. Subsequent treatment with this medicinal product should be based on a thorough assessment of the risks and benefits.

Neutralising antibodies

Neutralising antibodies may occur with the use of this medicinal product. If treatment with this medicinal product does not result in adequate haemostasis, then the development of neutralising antibodies should be suspected as the possible cause and, as clinically indicated, testing should be performed.
Neutralising antibodies to other Factor VIIa-containing products have been observed in congenital Factor VII-deficient patients, an unapproved indication for eptacog beta (activated).

Elderly

The safety and efficacy of this medicinal product have not yet been established in elderly patients. No data are available.

Patients with renal or hepatic impairment

The safety and efficacy of this medicinal product have not yet been established in patients with renal or hepatic impairment. No data are available.

Sodium content

This medicinal product contains less than 1 mmol sodium (23 mg) per injection, that is to say essentially 'sodium free'.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been conducted with this medicinal product.

Clinical experience with pharmacologic use of other FVIIa-containing products indicates an elevated risk of thrombotic events when used simultaneously with activated prothrombin complex concentrates (see section 4.4).
Based on a non-clinical study with eptacog alfa it is also not recommended to combine rFVIIa and rFXIII. There are no clinical data available on the interaction between rFVIIa and rFXIII.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data on the use of eptacog beta (activated) in pregnant women.

As a precautionary measure, it is preferable to avoid the use of this medicinal product during pregnancy.

Breast-feeding

It is unknown whether eptacog beta (activated) is excreted in human milk. No studies have been conducted to assess the impact of eptacog beta (activated) on milk production or its presence in breast milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from CEVENFACTA therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

Animal studies do not indicate direct or indirect harmful effect on male fertility. No fertility data are available in humans. Thus, the effect of eptacog beta (activated) on male and female fertility is unknown.

4.7 Effects on ability to drive and use machines

The active substance eptacog beta (activated) may have a minor influence on the ability to drive and use machines. Dizziness may occur following administration of the active substance eptacog beta (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

A total of 103 patients received at least one dose of eptacog beta (activated). The overall safety population used for the integrated analysis (see Table 3) comprised 75 unique patients, in four clinical studies, exposed to 3 418 injections in a total of 1 117 treatment episodes. The most frequently reported adverse reactions were infusion site discomfort (1.3%), infusion site haematoma (1.3%), post-procedural haematoma (1.3%), infusion-related reaction (1.3%), body temperature increased (1.3%), dizziness (1.3%) and headache (1.3%). Twenty-eight (28) other patients received a single intravenous bolus dose of eptacog beta (activated) in a fifth clinical study (Study LFB-FVIIA-009-19): a summary of the safety data from study LFB-FVIIA-009-19 is presented hereafter.

Paediatric population

Of the 75 patients included in the integrated analysis of safety, 34 were adolescents and children: 13 (17%) were aged <6 years, 15 (20%) were from 6 to less than 12 years and 6 (8%) were < 18 years.

The frequency, type, and severity of adverse reactions in children are expected to be the same as in adults.

Tabulated list of adverse reactions

In this section, the following categories of frequency have been used: 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 3 lists the adverse reactions.

Table 3: Adverse reactions from pooled clinical studies

System Organ Class	Adverse Reactions (Preferred Term)	Frequency
Nervous system disorders	Dizziness	Common
	Headache	Common
General disorders and administration site conditions	Injection site discomfort	Common
	Injection site haematoma	Common
Investigations	Body temperature increased	Common
Injury, poisoning and procedural complications	Post-procedural haematoma	Common
	Injection related reaction	Common

In study LFB-FVIIa-009-19, only one mild episode of headache (in the 75 µg/kg group) was assessed as related to eptacog beta (activated) and was resolved by the end of the study. There was no SAE. Overall, the safety data from Study 009-19 did not alter the CEVENFACTA safety profile described above.

Description of selected adverse reactions

Immunogenicity
In the pooled safety data for the three pivotal PerSept clinical studies, 5 out of 60 patients had a positive screening assay for anti-CEVENFACTA antibodies at baseline (prior to exposure to this medicinal product) and at follow-up visits. Two patients had transient anti-CEVENFACTA antibodies with an additional confirmatory test for anti-CEVENFACTA antibodies; these were confirmed as non-neutralising antibodies.

No patient developed anti-rabbit milk protein antibodies during treatment with this medicinal product. Still, as with all therapeutic proteins, there is the potential for immunogenicity.

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

There is no experience of overdose in clinical studies.
The dosing schedule should not be intentionally increased above the recommended doses due to the absence of information on the additional risk that may be incurred.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Blood coagulation factors, ATC code: B02BD08

Mechanism of action

In normal conditions, FVIIa is the factor initiating coagulation following its interaction with tissue-factor (TF) at the cell surface. Once the complex is formed, it activates mainly Factor X to Factor Xa and also factor IX to factor IXa. Activation of Factor X to Factor Xa initiates the common pathway of the coagulation cascade in which prothrombin is activated to thrombin, and then converts fibrinogen to fibrin to form a haemostatic plug, thereby achieving clot formation at the site of haemorrhage (haemostasis). This reaction is several-fold amplified in presence of factor VIII and factor IX.
In haemophilia A or B patients, factor VIII and factor IX molecules are absent or non-functional preventing coagulation amplification. This leads to debilitating bleeds that can sometimes be life threatening.
In these patients, FVIIa activates coagulation through the natural "TF-dependent" mechanism. However, the therapeutic doses required to reach haemostasis by using FVIIa are much more elevated than the normal FVII(a) circulating concentration. The presence of these supra-natural doses of FVIIa induces two additional coagulation pathways.
A second coagulation pathway "TF-independent" leads similarly than the "TF-dependent" mode of action to the generation of FXa at the surface of activated platelets, without the need of TF to anchor FVIIa at the cell surface and modify its structure. In addition, the use of high-FVIIa doses also alleviates the natural and constant inhibition of FVIIa by the FVII zymogen.
In a third pathway, FVIIa competes with activated protein C (aPC) by binding to the endothelial protein C receptor (EPCR). FVIIa thus down modulates the anticoagulation by limiting the cleavage of Factor Va, the FXa co-factor, by the aPC.
The combination of these three pathways allows FVIIa to bypass the need of FVIIIa or FIXa restoring haemostasis in their absence or even in the presence of inhibitors.

Pharmacodynamic effects

Laboratory assessments of coagulation do not necessarily correlate with or predict the haemostatic effectiveness of this medicinal product.

In the Phase 1b clinical study, this medicinal product demonstrated a dose and concentration-dependent pharmacodynamic effect on the coagulation system, including shortening of aPTT and PT, and increasing the thrombin generation test with platelets (TGT) and the maximum clot firmness (Fibrin-based Thromboelastometry).

Clinical efficacy and safety

The efficacy of this medicinal product was evaluated in three phase 3 clinical studies in a total of 60 male patients with congenital haemophilia A or B with inhibitors. The safety of this medicinal product was evaluated in these three clinical studies and also in the Phase 1b study (15 patients) and in an

additional clinical study with a PK assessment as the primary objective (28 patients), in a total of 103 unique male patients with congenital haemophilia A or B with inhibitors.

Efficacy in the treatment of bleedings in adults and adolescents:

PerSept 1 was a Phase 3, multicentre, open-label, randomised, crossover study of two initial dose regimens. The general objectives of this study were to assess the safety and efficacy of two dose regimens of the medicinal product across the full type of severity of bleeding episodes (mild, moderate, and severe), and to assess its pharmacokinetics. Per the study protocol patients ≥12 years of age (up to and including 75 years of age) with congenital haemophilia A or B with inhibitors to FVIII or FIX (positive inhibitor test BU threshold set at 5) were to be included.
Patients who met all entry criteria were randomised to start the study with either 75 µg/kg or 225 µg/kg treatment regimen of this medicinal product.
Twenty-seven adult and adolescent patients (≥12 years to less than 65 years of age) were included and evaluated for the treatment of 468 bleeding episodes with a median of 12 bleeding episodes per patient.

The results of an analysis of the proportion of successfully treated bleeding episodes with a "good" or "excellent" response (using a four-point rating scale), regardless of severity, at 12 hours after initial administration of this medicinal product (primary efficacy endpoint), with missing responses treated as failures are provided in Table 4.

Table 4: Proportion of bleeding episodes with a "Good" or "Excellent" response, regardless of severity, at 12 hours after initial administration of CEVENFACTA (treated population) – Missing responses treated as failures - PerSept 1 study

	Initial dose regimen at the time of bleeding episode		**Overall (N=27)**
	75 µg/kg (N=25)	**225 µg/kg (N=25)**	
Number of bleeding episodes	252	216	468
Number of successes	204 (81.0%)	195 (90.3%)	399 (85.3%)
Number of failures	48 (19.0%)	21 (9.7%)	69 (14.7%)
Success proportion [95% CI]	0.810 [0.709, 0.910]	0.903 [0.829, 0.977]	0.853 [0.770, 0.935]
p-value [1]	<0.001	<0.001	<0.001

Abbreviation: CI = confidence interval.
Notes: Table stratified by actual dose regimen at the time of the bleeding episode. Patients who completed Phase A without any safety concerns began treatment Phase B on the same CEVENFACTA treatment regimen that they were randomised to in Phase A (either 75 µg/kg or 225 µg/kg). Thereafter, the patient was crossed over to the alternate treatment regimen every 12 weeks until the end of the study.
[1] p-value from one-sided normal approximation test of H_0: $p \leq 0.55$, where p is the true proportion of successfully treated bleeding episodes at 12 hours, with adjustment for the correlation among bleeding episodes for a given patient. The test was conducted at the 0.0125 level (adjusted from 0.025 to 0.0125 to account for multiplicity of testing).
PerSept : Programme for the evaluation of recombinant factor Seven efficacy by prospective clinical trials.

In addition, at 24 hours, the majority of bleeding episodes was reported with a "good" or "excellent" assessment; the response was 96.7% [93.3%, 100%] and 99.5% [98.6%, 100%] with the 75 µg/kg and 225 µg/kg regimens respectively. The median time to attain a "good" or "excellent" assessment by the patient for a bleeding episode was 5.98 hours for the 75 µg/kg dosing regimen and 3 hours for the 225 µg/kg dosing regimen.

With regard to medicinal product consumption, a median of 1 and 2 injections was needed to treat a bleeding episode with the 225 and 75 µg/kg regimen respectively.

PerSept 2 was a Phase 3, global, multicentre, open-label, randomised, crossover study of two initial dose regimens. The general objectives of this study were to assess the safety and efficacy of two dose regimens of the medicinal product across the full type of severity of bleeding episodes (mild, moderate, and severe), and to assess its pharmacokinetics. The study included patients <12 years of age with congenital haemophilia A or B with inhibitors to FVIII or FIX (positive inhibitor test BU threshold set at 5).
Patients who met all entry criteria were randomised to start the study with either 75 µg/kg or 225 µg/kg of this medicinal product.
Twenty-five children (11.3 months to <12 years of age) were included and evaluated for the treatment of 549 bleeding episodes with a median of 17 bleeding episodes per patient.

Results of an analysis of the proportion of successfully treated bleeding episodes with a "good" or "excellent" response (using a four-point rating scale), regardless of severity, at 12 hours after initial administration of this medicinal product (primary efficacy endpoint), with missing responses treated as failures, are provided in Table 5.

Table 5: Proportion of bleeding episodes with a "Good" or "Excellent" response, regardless of severity, at 12 hours after initial administration of CEVENFACTA (treated population) - PerSept 2 study

	Initial dose regimen at the time of bleeding episode		
	75 µg/kg (N=23)	**225 µg/kg (N=24)**	**Overall (N=25)**
Number of bleeding episodes	239	310	549
Number of successes	158 (66.1%)	190 (61.3%)	348 (63.4%)
Number of failures	81 (33.9%)	120 (38.7%)	201 (36.6%)
Success proportion [95% CI]	0.661 [0.530, 0.792]	0.613 [0.487, 0.739]	0.634 [0.517, 0.751]
p-value[1]	0.048	0.164	0.080

Abbreviation: CI = confidence interval.
Notes: Table stratified by actual treatment regimen at the time of the bleeding episode. Patients who completed Phase A without any safety concerns began treatment Phase B on the same treatment regimen that they were randomised to in Phase A (either 75 µg/kg or 225 µg/kg). Thereafter, the patient was crossed over to the alternate treatment regimen every 12 weeks until the end of the study.
[1] p-value from one-sided normal approximation test of H_0: $p \leq 0.55$, where p is the true proportion of successfully treated mild/moderate/severe bleeding episodes at 12 hours, with adjustment for the correlation among bleeding episodes for a given patient. The test was conducted at the 0.0125 level (adjusted from 0.025 to 0.0125 to account for multiplicity of testing).
PerSept: Programme for the evaluation of recombinant factor Seven efficacy by prospective clinical trials

The efficacy results are considered inconclusive for PerSept 2: the primary efficacy endpoint was not met (i.e., the Objective Performance Criterion (OPC) was not exceeded). See section 4.2.

Efficacy in the prevention of bleedings in surgery and invasive procedures:

PerSept 3 was a Phase 3, multicentre, open-label, single-arm study that evaluated the safety and efficacy of this medicinal product in patients from ≥6 months to ≤75 years of age, who had haemophilia A or B with inhibitors to FVIII or FIX (positive inhibitor test BU threshold set at 5), and who were scheduled for an elective surgical or other invasive procedure. Twelve patients were enrolled in the study (6 in the minor surgery group and 6 in the major surgery group).
For a major surgical/invasive procedure, treatment was administered at an initial bolus dose of 200 µg/kg in a ≤2-minute intravenous injection immediately before the surgical incision or start of the invasive procedure. For a minor elective surgical/invasive procedure, this medicinal product was administered at an initial bolus dose of 75 µg/kg in a ≤2-minute intravenous injection immediately

before the surgical incision or start of an invasive procedure. For both minor and major procedures, administration was repeated no more frequently than every 2 hours at a dose of 75 µg/kg during and after the surgical/invasive procedure. The median duration of exposure was 18 days (major procedures) and 2.2 days (minor procedures).

The primary efficacy endpoint was the percentage of surgical or other invasive procedures with a "good" or "excellent" response to treatment 48 (±4) hours after the last administration of this medicinal product as assessed by the investigator. This assessment was based on the totality of assessments performed on the patient at each time point, also taking into consideration the surgeon's intraoperative haemostatic assessment, the number of (interventions for) bleeding episodes, oozing, blood transfusions, and the amount of medicinal product used. The primary analysis was based on non-missing assessments.

Six adults (up to 56 years old) and 6 paediatric patients (1 adolescent (14 years old) and 5 children (2 to 9 years old)) received this medicinal product for a total of 12 invasive procedures, of which 6 major and 6 minor. Four patients who previously participated in PerSept 1 (2 patients) and PerSept 2 (2 patients) were included in PerSept 3.

Of the 12 surgical procedures performed, 9 (81.8%) procedures were reported by the investigator as successfully treated ("good" or "excellent" response) at 48 hours after the last administration of this medicinal product, 2 (18.2%) were treatment failures ("poor" response), and 1 assessment was missing due to discontinuation of the study (withdrawal of consent) prior to the assessment at 48 hours.

The 2 treatment failures ("poor" response) were in the major surgery group. Response of one of them was imputed as "poor" due to discontinuation of the study following a TEAE leading to death (post-procedural haematoma within 2 days after the last dose of this medicinal product with anti-haemorrhagic rescue treatment within 52 hours after the last dose of this medicinal product): this was a patient who experienced 1 day after drug administration post procedural hematoma, then 3 days after drug administration serious gastrointestinal haemorrhage and serious blood loss anaemia, leading to death on the same day. The gastrointestinal haemorrhage and blood loss anaemia were initially reported as unlikely to be related and were subsequently updated to be probably related to the medicinal product by the investigator. Finally, following the independent Data Monitoring Committee (DMC)'s and Sponsor's reassessment, the causality assessment was considered as "unrelated". The other treatment failure required rescue treatment at postoperative Day 7 after which time he was determined to be a treatment failure.

The intraoperative haemostatic effect was rated as "excellent" or "good" for all 12 of the minor and major surgeries. The mean estimated actual intraoperative blood loss was lower compared to the mean maximum predicted blood loss (for a patient without a bleeding disorder undergoing the same procedure) for both minor surgeries (2.3 mL for actual intraoperative and 4.2 mL for maximum predicted) and major surgeries (270.0 mL and 350.0 mL, respectively).

5.2 Pharmacokinetic properties

The pharmacokinetic evaluation was conducted in clinical study LFB-FVIIA-009-19 in 28 patients with haemophilia A, with or without inhibitors to FVIII (mean age 37.2 (median of 15.1 (range 19-70 years)) who received a single dose of eptacog beta (activated) (either 75 µg/kg or 225 µg/kg).

This medicinal product displayed a pharmacokinetic profile comparable to other rhFVIIa products with an increase in plasma levels shortly after injection followed by a biexponential decay from the maximal concentration to return to baseline approximately 8-12 hours post-administration.

Data were analysed using noncompartmental analysis (NCA). Results of pharmacokinetic analysis after a single bolus intravenous administration of either 75 µg/kg or 225 µg/kg of this medicinal product in 28 adult patients are presented in Table 6.

Table 6: Pharmacokinetic parameters of CEVENFACTA (Geometric Mean [CV%]) in adults

Parameter (Geometric Mean (CV%))	C_{max} (ng/mL)	Clearance (L/h)	V_d (L)	$AUC_{0\text{-}inf}$ (ng*h/mL)	$t_{1/2}$ (h)
75 µg/kg (n=14)	938 (37)	5.1 (37)	8.2 (37)	1 008 (47)	2.3 (16)
225 µg/kg (n=14)	3 211 (23)	4.5 (20)	7 (22)	3 571 (26)	2.0 (8)

C_{max}= maximum plasma concentration; AUC0-inf = Area under the curve from time 0 to infinity; t½= terminal half-life; Vd= Volume of distribution

Non-compartmental analysis showed approximate dose proportionality between 75 µg/kg and 225 µg/kg of eptacog beta (activated), with the geometric mean AUC0-inf and C_{max} increasing 3.5- and 3.4-fold, respectively, for the 3.0-fold dose increment.

It should be noted that higher exposure (AUC and C_{max}) was observed for increasing body weight (especially relevant for obese subjects) for either of the available doses (75µg/kg and 225µg/kg). It is recognised that data in this subgroup is currently limited, but potential dosing recommendations will be updated once sufficient data will become available.

Limited pharmacokinetic data exist in the elderly: 3 elderly patients, from PK study LFB-FVIIA-009-19, were included in the clinical studies, 1 aged 70 years in the 75 µg/kg single intravenous dose arm, and 2 (the oldest aged 67 years) in the 225 µg/kg single intravenous dose arm.

No pharmacokinetic data in both renally-impaired and hepatically-impaired patients are available.

No clinical studies with this medicinal product to evaluate mass balance have been performed. Still, metabolism is expected to occur via proteolysis in the liver and excretion occurs in urine and faeces (amino acids) based on the available literature.

5.3 Preclinical safety data

All findings in the preclinical safety programme were related to the pharmacological effect of rFVIIa.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

Arginine hydrochloride
Isoleucine
Trisodium citrate dihydrate
Glycine
Lysine hydrochloride
Polysorbate 80
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.

6.3 Shelf life

3 years.

After reconstitution, the product must be stored in the vial and administered within 4 hours. Any unused solution should be discarded 4 hours after reconstitution.

For more information on instructions for reconstitution please refer to section 6.6.

6.4 Special precautions for storage

Store below 30 °C.
Do not freeze.
Keep the vial in the outer carton in order to protect from light.

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

6.5 Nature and contents of container and special equipment for administration

Each pack contains:

CEVENFACTA 1 mg (45 KIU) powder and solvent for solution for injection
- 1 glass vial with powder (1 mg) for solution for injection,
- 1 sterile vial adapter for reconstitution equipped with a 5 µm filter,
- 1 prefilled syringe of water for injections (1.1 mL),
- 1 plunger rod and backstop.

CEVENFACTA 2 mg (90 KIU) powder and solvent for solution for injection
- 1 glass vial with powder (2 mg) for solution for injection,
- 1 sterile vial adapter for reconstitution equipped with a 5 µm filter,
- 1 prefilled syringe of water for injections (2.2 mL),
- 1 plunger rod and backstop.

CEVENFACTA 5 mg (225 KIU) powder and solvent for solution for injection
- 1 glass vial with powder (5 mg) for solution for injection,
- 1 sterile vial adapter for reconstitution equipped with a 5 µm filter,
- 1 prefilled syringe of water for injections (5.2 mL),
- 1 plunger rod and backstop.

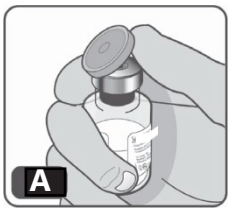
6.6 Special precautions for disposal and other handling

After reconstitution with the supplied set, the solution appears as a clear to slightly turbid colourless liquid free of foreign particles.
The reconstituted medicinal product should be inspected visually for particulate matter prior to administration. Do not use solutions that are cloudy or have deposits.

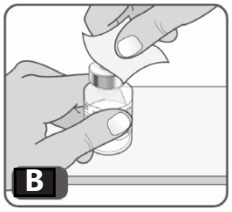
Instructions for reconstitution
Aseptic technique and a flat work surface should always be used during the reconstitution procedure.

1. CEVENFACTA powder vial and pre-filled syringe with solvent should be at room temperature (between 15 °C and 25 °C) at reconstitution**.**

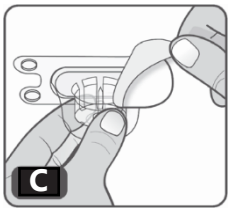
2. Remove the plastic cap from the vial (**Fig A**). If the cap is lost or missing, do not use the vial.



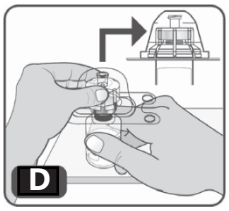
3. Wipe the rubber stopper on the vial with an alcohol swab. Allow the alcohol to dry. After cleaning with the swab, **do not touch the rubber stopper with your fingers and don't allow it to touch any other object until you attach the vial adapter, as this can transfer germs (Fig B)**.



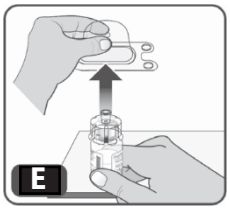
4. Open the vial adapter package by peeling off the protective paper cover, without touching the inside. Do not remove the vial adapter from the package. The spike of the adapter should line up with the middle of the grey rubber stopper (**Fig C**).



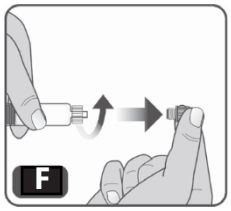
5. Turn the package over. Firmly press down to fully insert the vial adapter spike through the rubber stopper of the vial (**Fig D**).



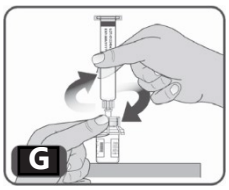
6. Lightly squeeze the plastic cover and lift up to remove it from the vial adapter. **Do not touch the exposed spike of the vial adapter (Fig E).**



7. Remove the syringe cap from the pre-filled syringe by holding the syringe body with one hand and using the other hand to unscrew the syringe cap (turn to the left). **Do not touch the syringe tip. Do not use the prefilled syringe if the syringe cap is lost or missing (Fig F).**

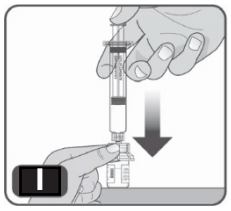


8. While holding the edges of the vial adapter screw on the prefilled syringe (turn to the right) a few turns until it starts to tighten. **Be careful not to overtighten as you will need to remove the syringe later (Fig G).**

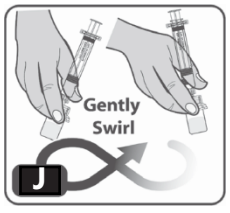


9. Hold the plunger rod by the wide top end in one hand and the syringe body using your other hand. Insert the plunger rod into the syringe, and then screw a few turns (turn to the right) so that the plunger rod is attached to the grey rubber stopper in the syringe (**Fig H).**

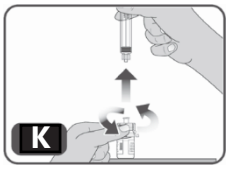
10. Very slowly push the plunger rod down to the bottom of the syringe, in order to transfer all of the liquid from the syringe into the vial. **Do not push too quickly as it can result in excess foam and air in the vial (Fig I).**



11. Swirl the vial gently or roll between hands until all powder is dissolved. **Do not shake the vial as this creates foam and air (Fig J).**



12. Without withdrawing any medicinal product back into the syringe, unscrew the syringe from the vial adapter (turn to the left) until it is completely detached. Don't remove the vial adapter from the vial (**Fig K**).



13. Withdraw the liquid medicinal product from the vial(s), using a syringe provided by your specialty pharmacy that is large enough to hold your prescribed dose.

If your dose requires more than one vial, repeat the above steps with additional kits until you have reached your required dose.

Instructions for administration

The medicinal product must be administered within 4 hours of reconstitution.
The medicinal product can be administered in 2 minutes or less as an intravenous infusion.

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

7. MARKETING AUTHORISATION HOLDER

Laboratoire français du Fractionnement et des Biotechnologies
Tour W
102 Terrasse Boieldieu, 19ème Étage
92800 Puteaux
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1664/001
EU/1/22/1664/002
EU/1/22/1664/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation:

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. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) 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

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR <THE CONDITIONAL MARKETING AUTHORISATION> <THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES>

A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

LFB Biomanufacturing
Quartier du Rieu
Avenue des Chênes Rouge
30100 Ales
France

Name and address of the manufacturer(s) responsible for batch release

LFB Biotechnologies
Zone d'activité des Courtabœuf
3 Avenue des Tropiques
91940 Les Ulis
France

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs 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.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

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

- **Risk management plan (RMP)**

The marketing authorisation holder (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 mg)

1. NAME OF THE MEDICINAL PRODUCT

CEVENFACTA 1 mg (45 KIU) powder and solvent for solution for injection

eptacog beta (activated)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

eptacog beta (activated) 1 mg/vial (45 KIU/vial), 1 mg/mL after reconstitution

3. LIST OF EXCIPIENTS

Powder: Arginine hydrochloride, Isoleucine, Trisodium citrate dihydrate, Glycine, Lysine hydrochloride, Polysorbate 80, Hydrochloric acid
Solvent: water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection
Each pack contains:
1 vial of powder,
1 syringe of sterile solvent,
1 plunger rod,
1 vial adapter.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single administration.
Administer within 4 hours of reconstitution.
Read the package leaflet before use.
Intravenous use.

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

9. SPECIAL STORAGE CONDITIONS

Store below 30 °C.

Do not freeze.
Keep the vial in the outer carton in order to protect from light.

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

Laboratoire français du Fractionnement et des Biotechnologies (LFB)
Tour W
102 Terrasse Boieldieu 19ème Étage
92800 Puteaux
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1664/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CEVENFACTA 1 mg

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

Powder vial (1 mg)

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

CEVENFACTA 1 mg (45 KIU) powder and solvent for solution for injection
eptacog beta (activated)
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 mg

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Pre-filled syringe with solvent (1.1 mL)

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

Solvent for CEVENFACTA 1 mg
water for injections
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1.1 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton (2 mg)

1. NAME OF THE MEDICINAL PRODUCT

CEVENFACTA 2 mg (90 KIU) powder and solvent for solution for injection

eptacog beta (activated)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

eptacog beta (activated) 2 mg/vial (90 KIU/vial), 1 mg/mL after reconstitution

3. LIST OF EXCIPIENTS

Powder: Arginine hydrochloride, Isoleucine, Trisodium citrate dihydrate, Glycine, Lysine hydrochloride, Polysorbate 80, Hydrochloric acid
Solvent: water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection
Each pack contains:
1 vial of powder,
1 syringe of sterile solvent,
1 plunger rod,
1 vial adapter.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single administration.
Administer within 4 hours of reconstitution.
Read the package leaflet before use.
Intravenous use.

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

9. SPECIAL STORAGE CONDITIONS

Store below 30 °C.

Do not freeze.
Keep the vial in the outer carton in order to protect from light.

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

Laboratoire français du Fractionnement et des Biotechnologies (LFB)
Tour W
102 Terrasse Boieldieu 19ème Étage
92800 Puteaux
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1664/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CEVENFACTA 2 mg

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

Powder vial (2 mg)

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

CEVENFACTA 2 mg (90 KIU) powder and solvent for solution for injection
eptacog beta (activated)
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2 mg

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Pre-filled syringe with solvent (2.2 mL)

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

Solvent for CEVENFACTA 2 mg
water for injections
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2.2 mL

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton (5 mg)

1. NAME OF THE MEDICINAL PRODUCT

CEVENFACTA 5 mg (225 KIU) powder and solvent for solution for injection

eptacog beta (activated)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

eptacog beta (activated) 5 mg/vial (225 KIU/vial), 1 mg/mL after reconstitution

3. LIST OF EXCIPIENTS

Powder: Arginine hydrochloride, Isoleucine, Trisodium citrate dihydrate, Glycine, Lysine hydrochloride, Polysorbate 80, Hydrochloric acid
Solvent: water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection
Each pack contains:
1 vial of powder,
1 syringe of sterile solvent,
1 plunger rod,
1 vial adapter.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For single administration.
Administer within 4 hours of reconstitution.
Read the package leaflet before use.
Intravenous use.

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

9. SPECIAL STORAGE CONDITIONS

Store below 30 °C.

Do not freeze.
Keep the vial in the outer carton in order to protect from light.

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

Laboratoire français du Fractionnement et des Biotechnologies (LFB)
Tour W
102 Terrasse Boieldieu 19ème Étage
92800 Puteaux
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/22/1664/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CEVENFACTA 5 mg

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

Powder vial (5 mg)

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

CEVENFACTA 5 mg (225 KIU) powder and solvent for solution for injection
eptacog beta (activated)
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5 mg

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Pre-filled syringe with solvent (5.5 mL)

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

Solvent for CEVENFACTA 5 mg
water for injections
IV

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5.2 mL

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

CEVENFACTA 1 mg (45 KIU) powder and solvent for solution for injection
CEVENFACTA 2 mg (90 KIU) powder and solvent for solution for injection
CEVENFACTA 5 mg (225 KIU) powder and solvent for solution for injection
eptacog beta (activated)

▼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. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What CEVENFACTA is and what it is used for

CEVENFACTA contains the active substance eptacog beta (activated), a recombinant human coagulation Factor VIIa (rhFVIIa).

CEVENFACTA is used in adults and adolescents (12 years of age or older) who were born with haemophilia A or B and who have developed inhibitors (antibodies). It is used for:
- the treatment of bleeding episodes,
- the management of bleeding during surgery.

How CEVENFACTA works
This medicine works by making the blood clot at the site of bleeding, when the body's own clotting factors are not working.

2. What you need to know before you use CEVENFACTA

Do not use CEVENFACTA
- if you are allergic to eptacog beta (activated), or any of the other ingredients of this medicine (listed in section 6),
- if you are allergic to rabbits or rabbit proteins.

Warnings and precautions
Before treatment with CEVENFACTA, tell your doctor:
- If you have a history of atherosclerosis (when your arteries are narrowed by disease), coronary artery disease (heart disease due to narrowing of the blood vessels supplying the heart),

cerebrovascular disease (disease of the blood vessels supplying the brain), a crush injury, septicaemia (serious blood infection) or blood clots;
- If you have heart disease, heart failure, abnormal heart rhythms;
- If you had prior pulmonary (lungs) clots or heart surgery;
- If you have or have had any other medical condition.

Patients with known allergy to casein may be at a higher risk of hypersensitivity reactions. Should signs or symptoms of hypersensitivity occur, treatment should be discontinued and you should seek immediate medical attention. Symptoms may include hives (itchy swellings under the skin), itching, rash, difficulty breathing, swelling around the mouth and throat, tightness of the chest, wheezing, dizziness or fainting, and low blood pressure.

Although the following conditions have not been observed, they may occur with CEVENFACTA:
- Blood clots in arteries in the heart (which could lead to a heart attack or angina), in the brain (which could lead to a stroke), or in the lungs or deep veins. Symptoms may include swelling and pain in the arms, legs or abdomen, chest pain, shortness of breath, loss of feeling or movement, and altered consciousness or speech.
- Hypersensitivity or anaphylactic reactions. Symptoms may include hives (itchy swellings under the skin), itching, rash, difficulty breathing, swelling around the mouth and throat, tightness of the chest, wheezing, dizziness or fainting, and low blood pressure.
- Inhibitors (antibodies) which may cause bleeding problems.

If any of these conditions apply to you, talk to your doctor before using CEVENFACTA.

It is important to keep a record of the batch number of your CEVENFACTA. So, every time you get a new package of CEVENFACTA, note down the date and the batch number (which is on the packaging after Lot) and keep this information in a safe place.

Adolescents
The listed warnings and precautions apply both to adults and adolescents (12 years of age and older).

Other medicines and CEVENFACTA
Tell your doctor if you are taking, have recently taken or might take any other medicines.

You should talk to your doctor before using CEVENFACTA if
- you are taking or have recently taken another activated Factor VII, or activated or non-activated prothrombin complex concentrates,
- you are taking or have recently taken Factor XIII,

since the combination of these medicines with CEVENFACTA may increase the risk of thromboembolic events (formation of blood clots in the veins).

You should talk to your doctor before using CEVENFACTA with these medicines.

Pregnancy, breast-feeding and fertility

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

Driving and using machines
Dizziness might occur following administration of CEVENFACTA. You must avoid driving or using machines while experiencing this symptom.

CEVENFACTA contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per injection, that is to say essentially ‘sodium free’.

3. How to use CEVENFACTA

Treatment with this medicine should be initiated and supervised by a physician experienced in the treatment of haemophilia and/or bleeding disorders.
CEVENFACTA comes as a powder that must be made up (reconstituted) with its solvent and injected into a vein (intravenous injection). See instructions for use guide at the end of this leaflet (section 7).

When to treat yourself
Injecting medicines requires special training. Do not attempt to self-inject unless you have been taught how to by your healthcare provider or haemophilia treatment centre.

Many people with inhibitors learn to self-inject or inject with the help of a family member: once trained, you will need additional injection equipment along with your CEVENFACTA kit so that you can successfully treat your bleeding episodes at home. Be sure to collect all necessary injection equipment before preparing the medicine for injection. This additional injection equipment will be provided by your healthcare professional (e.g., your pharmacist or haemophilia treatment centre).

CEVENFACTA may be injected at a haemophilia treatment centre, at your healthcare provider's office, or at home. Treating at the first sign of a bleed is important for bleed management.

Start treatment of a bleed as early as possible, ideally within 2 hours.
• In cases of a mild or moderate bleed (e.g., joint, superficial muscle, soft tissue, and mucous membranes), you should treat yourself as early as possible, ideally at home.
• In case of a severe bleed (e.g., life or limb [arm or leg] threatening haemorrhage, intracranial [within the skull] or gastrointestinal [in the stomach or gut] haemorrhage) you should contact your doctor.

Usually, severe bleeds are treated at the hospital and a dose of CEVENFACTA can be given on the way there.

Do not treat yourself for longer than 24 hours without consulting your doctor.
• Each time you use this medicine tell your healthcare provider as soon as possible.
• If bleeding is not controlled within 24 hours, contact your healthcare provider or emergency services immediately. You will usually need hospital care.

For instructions on reconstitution of the medicinal product before administration, follow the **Instructions For Use** guide at the end of this leaflet (section 7).
Inject the solution into your vein over 2 minutes or less.

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

Dose
Your healthcare provider will tell you how much CEVENFACTA to use, and when to use this medicine based on your weight, condition and type of bleed.

Treatment of bleeding episodes
Treatment with this medicine should be started as soon as a bleeding event occurs.

Mild and moderate bleeding

For mild to moderate bleeding episodes, treatment at home should not last longer than 24 hours. Continuing home treatment after 24 hours can only be considered after consultation with the haemophilia treatment centre.

Severe bleeding

You should seek immediate medical care if signs or symptoms of severe bleeding occur at home.

An initial dose can be administered on your way to the haemophilia treatment centre or your healthcare provider's office to avoid any treatment delay.

Always use this medicine exactly as described in this leaflet or as your doctor has told you. Check with your doctor if you are not sure.

Method of administration
For instructions on reconstitution of the medicinal product before administration and instructions on administration, follow the **Instructions For Use** guide at the end of this leaflet (section 7).

If you use more CEVENFACTA than you should
If you use too much CEVENFACTA, get medical advice at once.

If you forget to use CEVENFACTA,
If you forget to use CEVENFACTA, talk to your doctor.

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

4. Possible side effects

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

Common side effects
(may affect up to 1 in 10 people)
- Dizziness
- Headache
- Injection site discomfort
- Injection site bruising (haematoma)
- Body temperature increased
- Post procedural haematoma
- Injection related reaction

Reporting of side effects
If you get any side effects, talk to your doctor. 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 CEVENFACTA

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 label and the carton after EXP. The expiry date refers to the last day of that month.

Store below 30 °C.
Do not freeze.

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

To reconstitute CEVENFACTA only use the material provided in the kit.

After reconstitution, the product must be stored in the vial and given within 4 hours.
Any unused solution should be thrown away 4 hours after reconstitution.
Do not use this medicine if you notice the liquid has particles or is cloudy after mixing.

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 CEVENFACTA contains
- The active substance is recombinant coagulation factor VIIa (eptacog beta (activated))
- The other excipients are:
  Powder: arginine hydrochloride, isoleucine, trisodium citrate dihydrate, glycine, lysine hydrochloride, polysorbate 80, hydrochloric acid (for pH adjustment).
  Solvent: water for injections.
  See section 2 "CEVENFACTA contains sodium".

The powder for solution for injection contains: 1 mg/vial (corresponding to 45 KIU/vial), 2 mg/vial (corresponding to 90 KIU/vial), 5 mg/vial (corresponding to 225 KIU/vial).
After reconstitution the solution concentration is approximately 1 mg/ mL (45 KIU/ mL) eptacog beta (activated). 1 KIU equals 1 000 IU (International Units).

What CEVENFACTA looks like and contents of the pack
The powder vial contains a white to off-white lyophilised powder and the prefilled syringe of solvent contains clear and colourless solution. The reconstituted solution should be clear to slightly opaque.

Each CEVENFACTA pack contains:
- 1 glass vial with powder for solution for injection,
- 1 sterile vial adapter for reconstitution equipped with a 5 µm filter,
- 1 prefilled syringe of water for injections,
- 1 plunger rod and backstop.

Pack sizes: 1 mg (45 KIU), 2 mg (90 KIU), and 5 mg (225 KIU).

Marketing Authorisation Holder
Laboratoire français du Fractionnement et des Biotechnologies
Tour W
102 Terrasse Boieldieu 19ème Étage
92800 Puteaux
France

Manufacturer
LFB Biotechnologies
Zone d'activité de Courtabœuf
3 Avenue des Tropiques
91940 Les Ulis
France
+33 1 69 82 70 10

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

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site:
http://www.ema.europa.eu

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.

INSTRUCTIONS FOR USE:

READ THESE INSTRUCTIONS CAREFULLY BEFORE YOU START USING CEVENFACTA

CEVENFACTA is supplied as a powder. Before injection it must be made up (reconstituted) with the solvent supplied in the syringe. The solvent is water for injections. The reconstituted CEVENFACTA must be injected into your vein (intravenous use only).

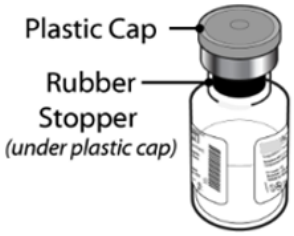
This kit provides the equipment needed to reconstitute this medicine. Additional materials are needed to inject the medicine after reconstitution. These materials will be provided by your healthcare professional (e.g., your pharmacist or haemophilia treatment centre).

Your doctor or your nurse will show you and/or your caregiver how to make up and inject CEVENFACTA. Do not use this kit without proper training by your healthcare provider or haemophilia treatment centre.

Use a clean and germ-free (aseptic) technique when preparing and injecting the medicine.

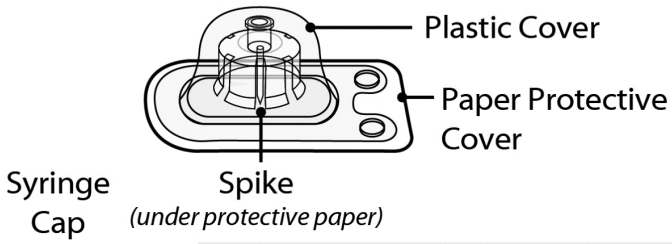
Your CEVENFACTA kit contains:
- 1 glass vial with powder for solution for injection
- 1 sterile vial adapter for reconstitution equipped with a 5 µm filter
- 1 prefilled syringe of water for injections
- 1 plunger rod and backstop

Powder Vial

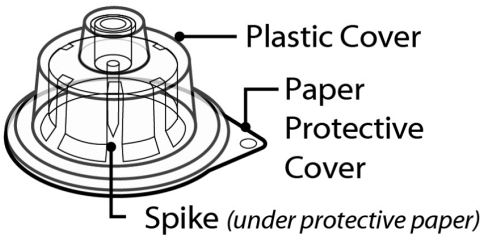


Vial Adapters* and Packaging

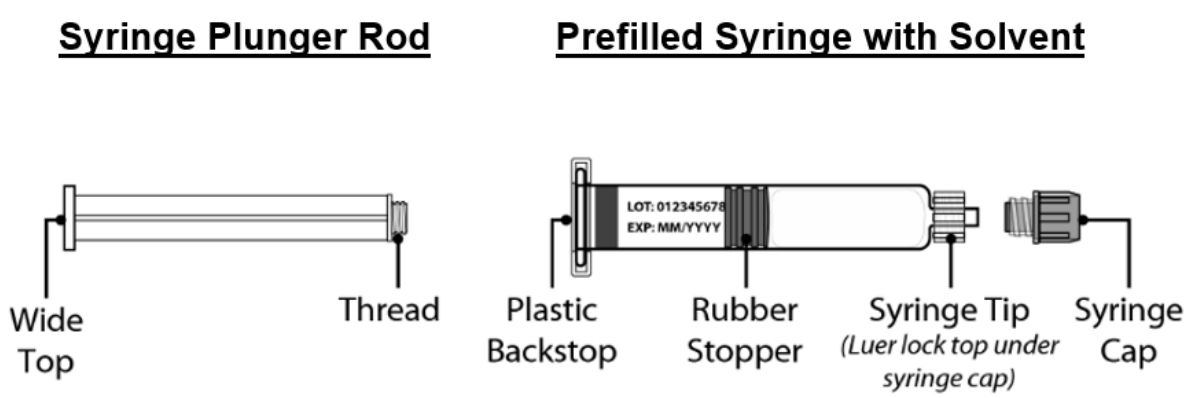
1mg and 2mg Vial Adapter



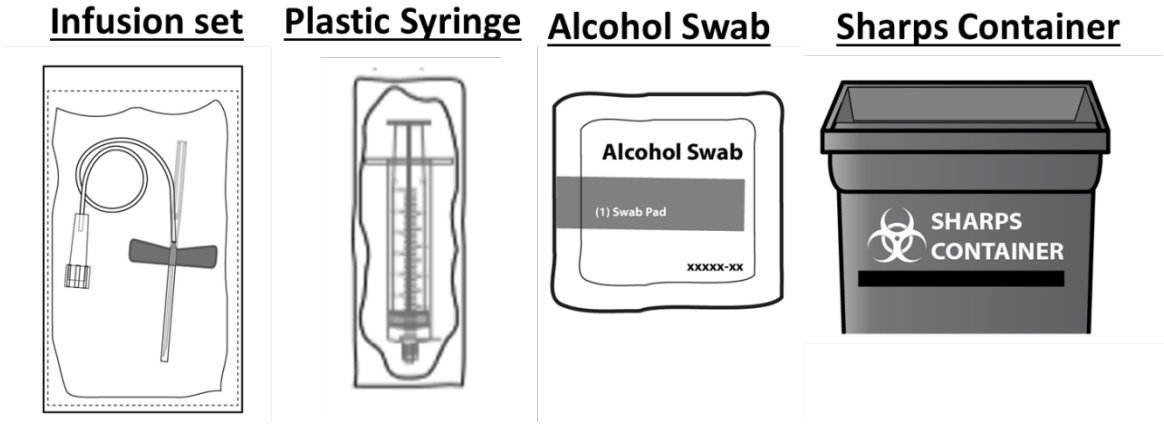
5mg Vial Adapter



**NOTE: Your CEVENFACTA kit will contain only one vial adapter.*



You will also need a sterile injection set (tubing and butterfly needle), a sterile plastic syringe, sterile alcohol swabs and a sharps container compliant with local applicable regulations and standards**. These materials are not included in the CEVENFACTA package.** These additional materials will be provided by your healthcare professional (e.g., your pharmacist or haemophilia treatment centre).



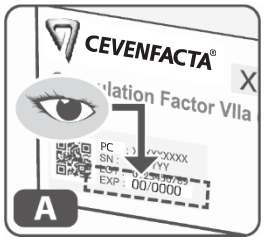
1) Collect equipment and prepare vial

- Take out the number of CEVENFACTA kits you need to fulfill your prescribed dose, a sterile injection set (not supplied) and an alcohol swab (not supplied).

Do not use the kit if the tamper seal has been broken or you suspect the kit is contaminated. Use a new kit instead.

- Check the expiry date on the side of the kit **(Fig. A)**.

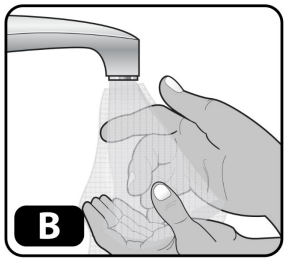
Do not use if the expiry date has passed.



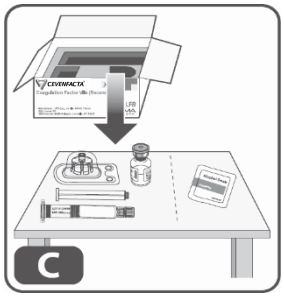
- Check the name, strength and colour of the package to make sure it contains the correct product (1 mg package is yellow, 2 mg package is green and 5 mg package is purple).

- Clean a flat surface before starting the steps for reconstituting CEVENFACTA.

- Wash your hands with soap and water and dry using a clean towel or air dry **(Fig. B)**.



- Take out the contents of one kit and one alcohol swab. Place items on the clean surface **(Fig. C)**.



- Inspect all contents of the kit. Make sure each vial has a matching coloured syringe.

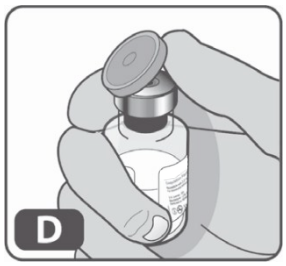
Do not use the contents if they have been dropped or if they are damaged. Use a new kit instead.

- If not already at room temperature, bring the vial and the pre-filled syringe to room temperature. You can do this by holding them in your hands until they feel as warm as your hands.

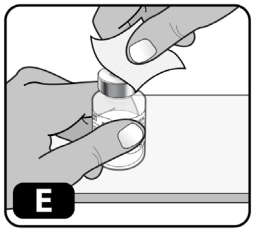
Do not warm the vial and pre-filled syringe in any other way.

- Remove the plastic cap from the vial **(Fig. D).**

If the plastic cap is loose or missing, do not use the vial.



- Wipe the rubber stopper with an alcohol swab **(Fig. E)** and allow it to air dry for a few seconds to ensure that it is as germ free as possible.

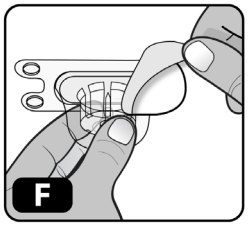


- After cleaning with the swab, **do not touch the rubber stopper with your fingers and do not allow it to touch any other object** until you attach the vial adapter, as this can transfer germs.

2) Attach vial adapter

- Peel off the protective paper cover from the vial adapter package **(Fig. F)**.

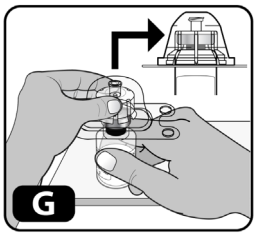
If the protective paper cover is not fully sealed or if it is broken, do not use the vial adapter.



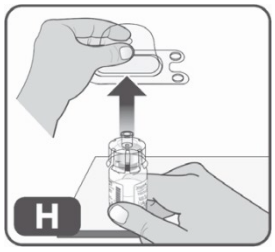
Do not take the vial adapter out of the protective cap with your fingers. If you touch the spike on the vial adapter, you may transfer germs from your fingers onto the spike.

- Place the vial on a clean flat surface and hold with one hand. Use your other hand to hold the plastic cover (with the vial adapter inside) directly over the vial and line up the spike of the adapter with the middle of the grey rubber stopper.

- Firmly press the plastic cover down so that the vial adapter spike breaks through the rubber stopper (you may hear/see it "snap" into place) **(Fig. G).**



- Lightly squeeze the plastic cover and lift it up to remove it from the vial adapter **(Fig. H)**.



Do not touch the top of the vial adapter once you have removed plastic cover to avoid transferring germs from your fingers.

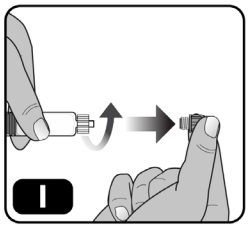
NOTE: The 5 mg vial adapter may not sit flat against the vial, but it is fully functional. As mentioned previously, your CEVENFACTA kit will contain only one vial adapter: the one suitable for the vial included in the kit.

3) Attach pre-filled syringe and install the plunger rod

- Remove the syringe cap from the pre-filled syringe by holding the syringe body with one hand and using the other hand to unscrew the syringe cap (turn to the left) **(Fig. I)**.

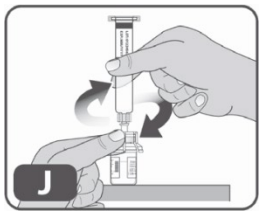
Do not touch the syringe tip under the syringe cap to avoid transferring germs from your fingers.

Do not use the pre-filled syringe if the syringe cap is loose or missing.



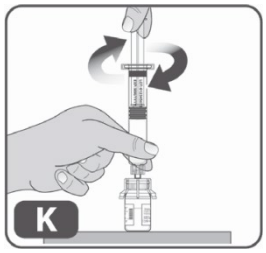
- Hold the edges of the vial adapter and screw on the pre-filled syringe (turn to the right a few times) until it starts to tighten **(Fig. J)**.

Be careful not to overtighten as you will need to remove the syringe later.



- To attach the plunger rod onto the syringe, hold the wide top end of the plunger rod in one hand and the syringe body in your other hand.

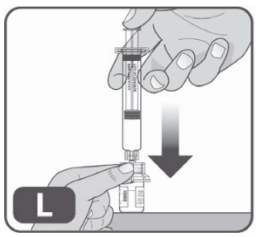
- Insert the plunger rod into the syringe, then screw a few turns (turn to the right) so that the plunger rod is attached to the grey rubber stopper in the syringe **(Fig. K)**.



4) Mix medicinal product in vial

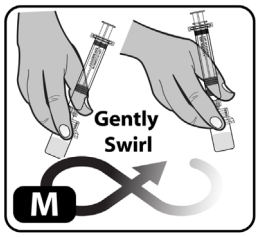
- Very slowly push the plunger rod down to the bottom of the syringe, to transfer all of the liquid from the syringe into the vial **(Fig. L)**.

Do not push too quickly as it can result in excess foam and air in the vial.



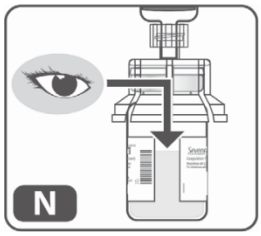
- Swirl the vial gently or roll between hands until all powder is dissolved **(Fig. M)**.

Do not shake the vial as this creates foam and air.



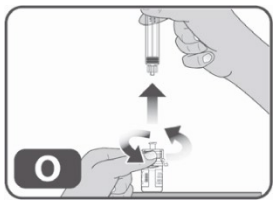
- Check the mixed solution **(Fig. N)**. It should be clear to slightly opaque. All powder should be dissolved with no particles floating in the liquid.

Do not use the medicinal product if the liquid has particles or is cloudy after mixing. Start over with a new kit.



5) Remove empty syringe from vial adapter

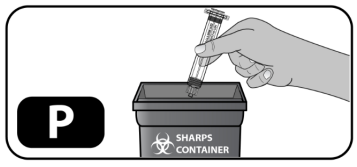
- Without withdrawing any medicinal product back into the syringe, unscrew the syringe from the vial adapter (turn to the left) until it is completely detached **(Fig. O)**.



- Throw out the empty syringe into an approved sharps container **(Fig. P)**.

Do not remove the vial adapter.

Do not touch the luer lock top of the vial adapter. If you touch this top, you may transfer germs from your fingers.



6) Mix additional vial(s) and inject dose

- If your dose requires more than one vial, repeat the above steps with additional kits until you have reached your required dose.

- Withdraw the liquid medicinal product from the vial(s), using a sterile syringe provided by your pharmacy that is large enough to hold your prescribed dose.

- CEVENFACTA must be administered within 4 hours of reconstitution **(Fig. Q)**.

Do not use if more than 4 hours have passed since reconstitution.

- CEVENFACTA can be given as an injection into your vein over the course of 2 minutes or less, according to the instructions given by your healthcare provider.

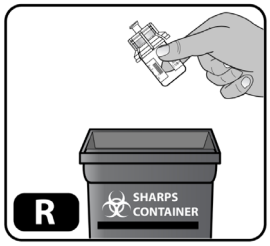
7) Throw out empty medicinal product vial(s)

- After reconstitution and injection, safely dispose of the vial with the vial adapter attached, the injection syringe, and any other waste materials into an approved sharps container **(Fig. R)**.

Do not throw out with ordinary household waste.

Do not take the vial and vial adapter apart before disposal.

Do not reuse any components of the kit.



Follow local applicable regulations and standards for proper disposal of the sharps container.

Storage

CEVENFACTA is supplied in a kit that should be stored below 30 °C.
Do not open the kit contents until you are ready to use them.
Do not freeze or store syringes containing reconstituted CEVENFACTA solution.
Avoid exposure of the reconstituted CEVENFACTA solution to direct light.

Important information

CEVENFACTA is only for injection into a vein (intravenous administration). Do not inject in any other way such as below the skin (subcutaneously) or into a muscle (intramuscularly). Contact your doctor, nurse or pharmacist if you experience problems.