CEVENFACTA®

Eptacog beta (activated)

in Practice

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));[1]
- 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.[1]

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Medical Information, Pharmalex, Tel: 01628 531171 medinfo.uk@pharmalex.com

Prescribing Information can be found on page 11

FOR HEALTHCARE PROFESSIONALS ONLY

Date of preparation: July 2023
23-07-004

LFB
ETHICAL COMMITMENT

CEVENFACTA®
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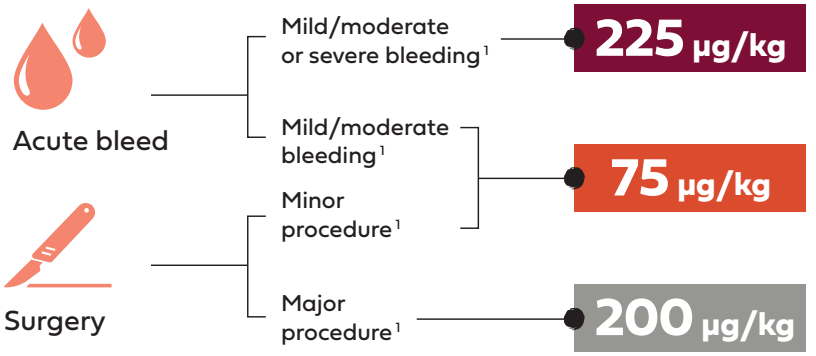
CEVENFACTA® stops the bleed, not the patient:

- Simple reconstitution [1]
- Can be self-administered at home* in ≤2 minutes [1]
- Comprehensively evaluated in the 3 global, multicentre clinical trials of the PERSEPT programme [4]
- Provides sustained control of acute bleeding episodes and surgical bleeding with a fast onset of action [1,2,3]

*: After training by a healthcare professional or haemophilia treatment centre. [5]

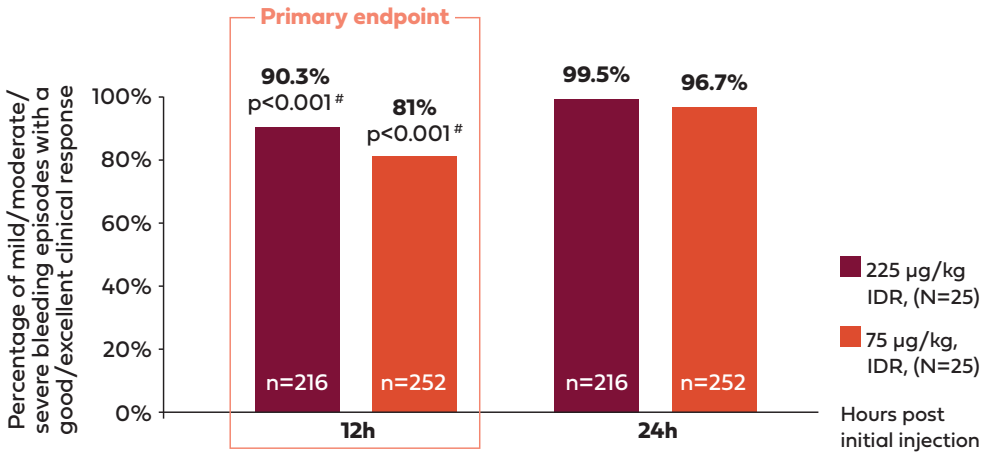
CEVENFACTA® has 3 initial dosing regimens (IDRs)



Subsequent dose(s) of **75 µg/kg** may be required to control bleeding episodes for all regimens; please refer to the SmPC[1] for more details. If an adequate haemostatic response is not achieved within 24 hours, alternative therapies should be considered.

Sustained and reliable control of bleeding episodes

CEVENFACTA® PROVIDES "GOOD/EXCELLENT" EFFICACY AT 12H AND 24H *[1,2]



N: Number of subjects; n: Number of bleeding episodes; missing data counted as failures
Adapted from CEVENFACTA® SmPC[1] and Wang *et al.* 2017[2]

*: PERSEPT 1 was a global, prospective, multicentre, phase 3, randomised, open-label, cross-over study of 2 IDRs for the on-demand early treatment and control of bleeding episodes in patients aged 12-75 years with congenital haemophilia A or B and inhibitors to FVIII or FIX. The primary endpoint was the proportion of successfully treated bleeding episodes regardless of severity at 12 hours after initial CEVENFACTA® administration and without rebleeding prior to 24 hours.[1,2]

#: P-value from one-sided normal approximation test of p, 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 subject.[2]

IDR: Initial dose regimen; **SmPC:** Summary of product characteristics

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Dose regimens for the treatment of bleeding episodes[1]

Start treatment of a bleed as early as possible, ideally within 2 hours[1]

Mild/moderate bleeding

IDR

75 µg/kg

Wait 3 hours

If bleeding is not controlled, inject **75 µg/kg every 3 hours** until haemostasis is achieved

225 µg/kg

Wait 9 hours

If bleeding is not controlled, inject **75 µg/kg every 2 hours** until haemostasis is achieved

- For mild-to-moderate bleeding episodes, the duration of home therapy should not exceed 24 hours.
- If bleeding is not controlled within 24 hours, patients must contact their healthcare professional or the emergency services immediately.

Severe bleeding

IDR

225 µg/kg

Wait 6 hours

If bleeding is not controlled, inject **75 µg/kg every 2 hours** until haemostasis is achieved

- Patients should seek immediate medical care if signs or symptoms of severe bleeding occur at home.
- Severe bleeds should be treated at hospital; an initial dose of CEVENFACTA® can be administered on the way there to avoid any treatment delay.

Dose regimens for perioperative management of bleeding[1]

	Minor surgical procedure[1]	**Major surgical** procedure[1]
Initial dose / Pre-operative dose	**75 µg/kg** immediately before surgery or at start of invasive procedure	**200 µg/kg** immediately before surgery
Subsequent dose(s) / Operative dose(s)	**75 µg/kg** repeated every **2 hours** for the **first 48 hours**	**75 µg/kg** every **2 hours** for the duration of the surgery
Post-operative dose(s)		**75 µg/kg** every **2 hours** — First 48 hours **75 µg/kg** every **2 to 4 hours** — Days 3-4 **75 µg/kg** every **2 to 6 hours** — Days 5-6 **75 µg/kg** every **2 to 8 hours** — Days 7-10 **75 µg/kg** every **2 to 12 hours** — Day 11 onwards

- Most minor procedures should be treated for 48 hours to achieve haemostasis.
- At the discretion of the health care professional, CEVENFACTA® may be administered less frequently than every 2 hours and/or for less than 48 hours.

Following the surgery, CEVENFACTA® (75 µg/kg) is also recommended prior to drain or suture removal or physical therapy.

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.[1]

Contraindications: Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the CEVENFACTA® SmPC, or to rabbits or rabbit proteins.[1]
Please refer to CEVENFACTA® SmPC for special warnings and precautions for use.[1]

Common AEs from Pooled Clinical trials: Dizziness, headache, injection site discomfort, injection site haematoma, body temperature increased, post-procedural haematoma, injection related reaction.

A complete list of AEs is available in the SmPC[1]

AE: Adverse event; **IDR**: Initial dose regimen; **SmPC**: Summary of Product Characteristics.

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Dose calculation

$$\text{Dose (mg)} = \frac{\text{dosing regimen (µg/kg) x weight (kg)}}{1000}$$

Weight (kg)	TREATMENT OF ACUTE BLEEDING EPISODES		PERIOPERATIVE MANAGEMENT OF BLEEDING	
	Mild/moderate 75 µg/kg	All severity 225 µg/kg	Minor surgery 75 µg/kg	Major surgery 200 µg/kg
	Initial dose (mg)	Initial dose (mg)	Initial dose (mg)	Initial dose (mg)
30	2.25	6.75	2.25	6
35	2.625	7.875	2.625	7
40	3	9	3	8
45	3.375	10.125	3.375	9
50	3.75	11.25	3.75	10
55	4.125	12.375	4.125	11
60	4.5	13.5	4.5	12
65	4.875	14.625	4.875	13
70	5.25	15.75	5.25	14
75	5.625	16.875	5.625	15
80	6	18	6	16
85	6.375	19.125	6.375	17
90	6.75	20.25	6.75	18
95	7.125	21.375	7.125	19
100	7.5	22.5	7.5	20

Two vial sizes currently available:

*: 45,000 IU; #: 225,000 IU

Equipment for reconstitution and injection

CEVENFACTA® is supplied ready for reconstitution[1]

- Glass vial with powder for solution for injection
- Prefilled syringe of sterile water for injection
- Plunger rod
- Sterile vial adapter

The equipment for injection is not supplied in the product package. A suitably sized sterile syringe, sterile injection set (tubing and butterfly needle), sterile cloth and swabs, disinfectant wipes and a plaster are typically required.

Before reconstitution[1]

- Shelf life of the product: **3 years** when stored **below 30°C.**
- Keep powder and solvent in the outer carton protected from light.
- **Do not freeze.**

After reconstitution[1]

- The solution should be stored in the vial **below 30°C.**
- It must be administered **within 4 hours.**
- Any unused solution should be **discarded 4 hours after reconstitution.**

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4 steps to reconstitute CEVENFACTA®[1]

1 Collect supplies and prepare vial[1]

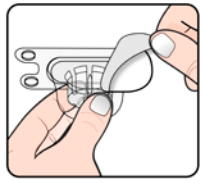
Before starting reconstitution, check the expiration date; do not use if the expiration date has passed. Check the brand name, strength and colour of the package to make sure it contains the correct product (1 mg package is yellow and 5 mg package is purple).

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. Take out the contents of one pack and place items on the clean surface. CEVENFACTA® powder vial and pre-filled syringe with solvent should be at room temperature (between 15°C and 25°C).

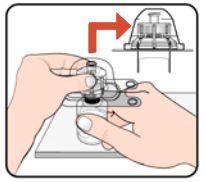
Remove the plastic cap from the vial.
- Don't use the vial if the cap is loose or missing.

Wipe the rubber stopper with an alcohol swab and allow to air dry for a few seconds.
- Don't touch the rubber stopper anymore.

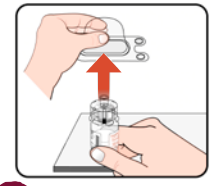
2 Attach the vial adapter[1]



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

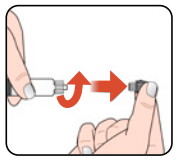


With one hand, hold the vial on the surface. With the other hand, place the plastic cover over the vial. The spike of the adapter should line up with the middle of the stopper. Firmly press down to fully insert the vial adapter spike through the rubber stopper of the vial.



Lightly squeeze the plastic cover and lift up to remove it from the vial adapter.
- Do not touch the top of the vial adapter once the plastic cover is removed to avoid transferring germs from your fingers.

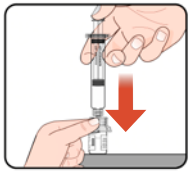
3 Attach the pre-filled syringe and insert plunger rod[1]

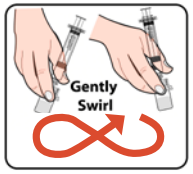


Remove the cap from the pre-filled syringe by unscrewing to the left.
Screw the pre-filled syringe onto the vial via the adapter by turning to the right.
- Be careful not to screw it in too tightly.

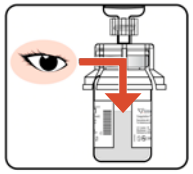
Insert the plunger rod into the syringe, then screw a few turns to the right so that the plunger rod is attached to the rubber stopper in the syringe.

4 Mix the powder with the sterile solution[1]



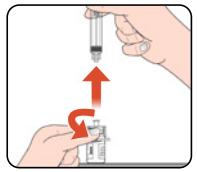


Push the plunger down slowly to transfer all of the liquid from the syringe into the drug vial. Swirl the vial gently or roll between your hands until all the powder is completely dissolved.
- Do not shake the vial.



Check the solution is correctly mixed, it should be clear to slightly opaque.
- If there are particles or the solution is cloudy after mixing, do not use it.

Without withdrawing any drug back into the syringe, unscrew the syringe from the vial adapter (turn to the left) until it is completely detached.
- Do not remove the vial adapter from the vial.



If the patient requires more than one vial, repeat the above steps with additional packs you have reached the required dose.

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Administration of CEVENFACTA®

Once reconstituted, withdraw the liquid drug from the vial(s), using a sterile syringe that is large enough to hold the total prescribed dose. The equipment for injection is not supplied in the product package. A suitably sized sterile syringe, sterile injection set (tubing and butterfly needle), sterile cloth and swabs, disinfectant wipes and a plaster are typically required.[1]

CEVENFACTA® should be administered in 2 minutes or less as an intravenous bolus injection.[1]

CEVENFACTA® may be self-administered at home by the patient providing they have been suitably trained by a healthcare professional.[5] LFB also provide a guide booklet to support patients who have been prescribed CEVENFACTA®.

KEY REMINDERS FOR PATIENTS WHO SELF-ADMINISTER[1,5]

- CEVENFACTA® must be administered within 4 hours of reconstitution
- Do not throw away the product in the ordinary household waste.
- Do not open the kit contents until you are ready to use them.
- Do not reuse any components of the kit.
- CEVENFACTA® must not be mixed with other medicinal products.
- CEVENFACTA® is for intravenous administration only. Do not administer by any other route (subcutaneous or intramuscular).

More information for patients is available in the CEVENFACTA® Patient Guide

Prescribing Information

CEVENFACTA▼ (eptacog beta (activated)) 1mg/5mg Powder and 1.1mL/5.2mL solvent for solution for intravenous injection. This medicinal product is subject to additional monitoring to allow quick identification of new safety information.

Consult Summary of Product Characteristics (SmPC) before prescribing

Indications: Treatment of bleeding episodes and prevention of bleeding in adults and adolescents (≥12 years of age) undergoing surgery or invasive procedures:

- 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.

Treatment should be initiated/supervised by a physician experienced in haemophilia. Dose and duration of treatment depend on location/severity of bleeding or type of surgery/procedure, need for urgent haemostasis, frequency of administration, known responsiveness to FVIIa-containing bypassing agents during prior bleeding events. Results of laboratory assessments of coagulation (PT, INR, aPTT, FVII:C) do not necessarily correlate with/predict haemostatic effectiveness of this medicine. Maximum tolerated doses have not been determined and cumulative daily doses >1025 µg/kg have not been studied. Initiate treatment as soon as bleeding occurs. For mild/moderate bleeding episodes, home therapy should not exceed 24 hours. If severe bleeding occurs in home setting, immediate medical care should be sought. To avoid treatment delay, an initial dose can be administered at home. If an adequate haemostatic response is not achieved e.g. within 24 hours for mild/moderate bleeding episodes, alternative therapies should be considered.

Dosage and administration:
Bleeding Episodes

Type of bleeding	Dosing Recommendation
Mild and moderate	75 µg/kg repeated every 3 hours until haemostasis is achieved. or 225 µg/kg initially. If haemostasis is not achieved within 9 hours, additional 75 µg/kg doses may be administered every 3 hours as needed to achieve haemostasis. Continue therapy to support healing and prevent recurrent haemorrhage after haemostasis to maintain haemostatic plug. Site and severity of bleeding should determine therapy duration.
Severe	225 µg/kg initially, followed if necessary 6 hours later with 75 µg/kg every 2 hours until haemostasis is achieved. Continue therapy to support healing and prevent recurrent haemorrhage. Site and severity of bleeding and use of other procoagulant therapies should determine treatment duration.

Perioperative Management

Type of surgical procedure	Dosing Recommendation
Minor	75 µg/kg immediately before surgery or start of invasive procedure; then 75 µg/kg repeated every 2 hours for the first 48 hours following the initial dose.
Major	200 µg/kg immediately before the surgery, followed by 75 µg/kg every 2 hours for the duration of the surgery. 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

Following surgery, 75 mcg/kg also recommended prior to drain/suture removal or physical therapy.

Dosing regimen in elderly and in those with renal/hepatic impairment not yet established.

Method of administration: For reconstitution instructions, see SmPC. Administer as intravenous bolus injection over 2 minutes or less.

Contra-indications: Hypersensitivity to the active substance or excipients. Hypersensitivity to rabbits or rabbit proteins.

Warnings and Precautions: *Traceability:* Record name and batch number. *Thrombosis:* May be an increased risk of thromboembolic events if history of congenital or acquired haemophilia receiving concomitant treatment with aPCC/PCC or other haemostatic agents or with history of atherosclerosis, coronary artery disease, cerebrovascular disease, crush injury, septicaemia or thromboembolism. Monitor closely for signs or symptoms of activation of the coagulation system or thrombosis. If laboratory confirmation of intravascular coagulation or presence of thrombosis, reduce or stop Cevenfacta, depending on patient's condition. *Hypersensitivity reactions*: Hypersensitivity reactions, including anaphylaxis, may occur – treatment should be discontinued and immediate medical attention sought. Patients with known IgE-based hypersensitivity to casein may be at a higher risk of hypersensitivity reactions. *Neutralising antibodies:* If treatment does not result in adequate haemostasis, test for neutralising antibodies.

Interactions: None known. Clinical experience with other FVIIa products indicates elevated risk of thrombotic events when used simultaneously with aPCC. It is not recommended to combine this product with aPCC or rFXIII.

Pregnancy and lactation: No data. Avoid use during pregnancy. Discontinue breastfeeding or discontinue/abstain from Cevenfacta during breastfeeding.

Effects on driving/using machinery: Minor influence - dizziness may occur after administration.

Undesirable effects: Consult SmPC for full details. Common (>1/100 to <1/10): Injection site discomfort, injection site haematoma, post-procedural haematoma, injection-related reaction, body temperature increased, dizziness and headache.

Legal Category: POM

Package Quantities and Basic NHS Price: 1mg vial £525.20, 5mg vial £2626

Marketing Authorisation Holder:

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

Marketing Authorisation Number: PLGB 17469/0011 (1mg), PLGB 17469/0013 (5mg)

Further information is available from LFB Biopharmaceuticals Limited, Suite 104, Spirella Building, Bridge Road, Letchworth Garden City, SG6 4ET Tel: +44(0) 1462 558844

Date of preparation: September 2022

CEVENFACTA®

Eptacog beta (activated)

Stop the bleed Not the patient

REFERENCES:

1. CEVENFACTA® Summary of Product Characteristics. **2.** Wang M. *et al.* PERSEPT 1: a phase 3 trial of activated eptacog beta for on-demand treatment of haemophilia inhibitor-related bleeding. Haemophilia. 2017;23:832–843. **3.** Escobar M. *et al.* PERSEPT 3: A phase 3 clinical trial to evaluate the haemostatic efficacy of eptacog beta (recombinant human FVIIa) in perioperative care in subjects with haemophilia A or B with inhibitors. Haemophilia 2021;27:911–20. **4.** Escobar M. *et al.* The safety of activated eptacog beta in the management of bleeding episodes and perioperative haemostasis in adult and paediatric haemophilia patients with inhibitors. Haemophilia. 2021; 27:921–931. **5.** CEVENFACTA® Patient Information Leaflet.

For medical information, contact **medinfo.uk@pharmalex.com**
More information can be found at **www.cevenfacta.co.uk**

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