Medicines & Healthcare products Regulatory Agency

MHRA

Public Assessment Report

National Procedure

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

eptacog beta (activated)

PLGB 17469/0011-0013

Laboratoire français du Fractionnement et des Biotechnologies

LAY SUMMARY

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

This is a summary of the Public Assessment Report (PAR) for CEVENFACTA 1 mg (45 KIU), 2mg (90 KIU), 5mg (225 KIU) powder and solvent for solution for injection. It explains how these products were assessed and their authorisation recommended, as well as their conditions of use. It is not intended to provide practical advice on how to use these products.

These products will be referred to as Cevenfacta in this lay summary for ease of reading.

For practical information about using Cevenfacta, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Cevenfacta and what is it used for?

These products have been authorised by MHRA for Great Britain (consisting of England, Scotland and Wales). In coming to its decision, MHRA has relied on a European Commission (EC) decision on 15 July 2022 (EMEA/H/C/005655), in accordance with the advice from the Committee for Medicinal Products for Human Use (CHMP). This is known as the EC Decision Reliance Procedure.

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 does Cevenfacta work?

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

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

How is Cevenfacta used?

The pharmaceutical form of these medicines is a powder for solution for injection and the route of administration is injection into a vein (intravenous use).

Cevenfacta can only be obtained with a prescription and treatment must be started and supervised by a doctor who is experienced in the treatment of haemophilia or bleeding disorders.

For the treatment of bleeding episodes, an initial dose should be given as soon as possible after the first sign of a bleed. For mild to moderate bleeds, patients can be given a starting dose of 225 microgram per kilogram body weight and, if the bleeding is not controlled after 9 hours, doses of 75 microgram per kilogram should be given every 3 hours until the bleed is controlled. Patients can also start on 75 micrograms per kilogram, repeated every 3 hours until control of the bleed. For severe bleeds, patients should be given 225 micrograms per

kilogram and, if the bleeding is not controlled within 6 hours after the first dose, doses of 75 microgram per kilogram should be given every 2 hours until the bleed is controlled.

For the prevention of bleeding during surgical or other medical procedures, Cevenfacta is given before and during the procedure, and in some cases for several days after, with the dose depending on the type of surgery.

Patients or caregivers may be able to give Cevenfacta themselves after suitable training, but treatment at home should not exceed 24 hours without consulting the treating doctor.

For further information on how Cevenfacta is used, refer to the PIL and Summaries of Product Characteristics (SmPCs) available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

These medicines can only be obtained with a prescription.

The patient should always take the medicine exactly as their doctor/pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

What benefits of Cevenfacta have been shown in studies?
The benefits of Cevenfacta were evaluated in a main study in adults and adolescents (over 12 years of age) with haemophilia A or B with inhibitors. In this study, Cevenfacta was not compared with another treatment.

Twenty-seven patients were given Cevenfacta after bleeding episodes, and in 81.0 % (204 out of 252) of the episodes treated with a lower dose (75 microgram per kg of patient body weight) and 90.3 % (195 out of 216) of the episodes treated with a higher dose (225 microgram per kg of patient body weight) the symptoms had largely been reduced or had completely disappeared 12 hours after the first injection.

In another study which investigated Cevenfacta in the prevention of uncontrolled bleeding during and after surgical procedures, 12 patients with haemophilia A or B received the medicine before, during and after surgery. Two days after surgery, control of postoperative blood loss was considered good or excellent in 81.8 % (9 out of 12) of surgeries.

What are the possible side effects of Cevenfacta?
For the full list of all side effects reported with these medicines, see Section 4 of the PIL or the SmPCs available on the MHRA website.

If a patient gets any side effects, they should talk to their doctor, pharmacist or nurse. This includes any possible side effects not listed in the product information or the PIL that comes with the medicine. Patients can also report suspected side effects themselves, or a report can be made on their behalf by someone else who cares for them, directly via the Yellow Card scheme at https://yellowcard.mhra.gov.uk or search for 'MHRA Yellow Card' online. By reporting side effects, patients can help provide more information on the safety of this medicine.

The most common side effects with Cevenfacta (which may affect more than 1 in 100 people) are injection site discomfort and haematoma (a collection of blood under the skin) as well as injection related reactions, an increase in body temperature, dizziness and headache.

Cevenfacta must not be used in people who are hypersensitive (allergic) to eptacog beta (activated), to rabbits or rabbit proteins, or to any of the other ingredients.

Why was Cevenfacta approved?
MHRA decided that the benefits are greater than the risks and recommended that these medicines can be approved for use.

What measures are being taken to ensure the safe and effective use of Cevenfacta?
As for all newly-authorised medicines, a Risk Management Plan (RMP) has been developed for Cevenfacta. The RMP details the important risks of Cevenfacta, how these risks can be minimised, any uncertainties about Cevenfacta (missing information), and how more information will be obtained about the important risks and uncertainties.

The following safety concerns have been recognised for Cevenfacta:

Important identified risks:	None
Important potential risks:	Anaphylactic reactions Thromboembolic events Immunogenicity
Missing information:	Pregnant and breastfeeding women Patients with hepatic or renal impairment Elderly patients

Additional pharmacovigilance measures include participation in patient registries.

The information included in the SmPC and the PIL is compiled based on the available quality, non-clinical and clinical data, and includes appropriate precautions to be followed by healthcare professionals and patients. Side effects of Cevenfacta are continuously monitored and reviewed including all reports of suspected side-effects from patients, their carers, and healthcare professionals.

An RMP and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Other information about Cevenfacta
Marketing authorisations were granted in Great Britain on 19 August 2022.

The full PAR for Cevenfacta follows this summary.

This summary was last updated in February 2023.

TABLE OF CONTENTS

I. INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Medicines and Healthcare products Regulatory Agency (MHRA) considered that the applications for CEVENFACTA 1 mg (45 KIU), 2mg (90 KIU), 5mg (225 KIU) powder and solvent for solution for injection (PLGB 17469/0011-0013) could be approved.

The products are approved for the following indications:

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.

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 the 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.

These products have been authorised by MHRA for Great Britain (consisting of England,

Scotland and Wales). In coming to its decision, MHRA relied on a European Commission (EC) decision on 15 July 2022 (EMEA/H/C/005655), in accordance with the advice from the Committee for Medicinal Products for Human Use (CHMP).
For the scientific discussion of the quality, non-clinical and clinical assessment conducted by the European Medicines Agency (EMA), please refer to the European Public Assessment Report, available on the EMA website.

These applications were approved under Regulation 50 of the Human Medicines Regulation 2012, as amended (previously Article 8.3 of Directive 2001/83/EC, as amended).

The MHRA has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for these products at all sites responsible for the manufacture, assembly and batch release of these products.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with these applications and are satisfactory.

Marketing authorisations were granted on 19 August 2022

II. PRODUCT INFORMATION

SUMMARY OF PRODUCT CHARACTERISTICS (SmPC)

The SmPCs are in line with current guidelines and are satisfactory.

PATIENT INFORMATION LEAFLET

The PIL is in line with current guidelines and is satisfactory.

LABEL

The labelling is in line with current guidelines and is satisfactory.

III. QUALITY ASPECTS

MHRA considered that the quality data submitted for these applications is satisfactory.

The grant of marketing authorisations was recommended.

IV. NON-CLINICAL ASPECTS

MHRA considered that the non-clinical data submitted for these applications is satisfactory.

The grant of marketing authorisations was recommended.

V. CLINICAL ASPECTS

MHRA considered that the clinical data submitted for these applications is satisfactory.

The grant of marketing authorisations was recommended.

VI. RISK MANAGEMENT PLAN (RMP)

The applicant has submitted an RMP, in accordance with the requirements of Regulation 182 of The Human Medicines Regulation 2012, as amended. In addition to routine pharmacovigilance and risk minimisation measures, the following additional if applicable: pharmacovigilance measures have been proposed:

Anaphylactic reactions	
Evidence for linking the risk to the medicine	Hypersensitivity reactions and anaphylaxis have been observed in clinical trials and post-marketing setting with medicinal products of the same therapeutic class [*Novoseven EPAR, Novoseven EU PI*]. Important potential risk of anaphylactic reaction cannot be ruled out and must then be considered as a potential class effect
Risk factors and risk groups	Patients with known IgE-based hypersensitivity to rabbit proteins may be at higher risk of anaphylactic reactions.
Risk minimisation measures	SmPC sections 4.3 & 4.4 PL sections 2 & 4
Additional pharmacovigilance activities	Collaboration with EUHASS and PedNet patient registries

Thromboembolic events	
Evidence for linking the risk to the medicine	Venous and arterial thromboembolic events have been observed in clinical trials and post-marketing setting with medicinal products of the same therapeutic class [*Novoseven EPAR, Novoseven EU PI*]. Clinical experience with pharmacologic use of FVIIa-containing products indicates an elevated risk of serious thrombotic events when used simultaneously with activated prothrombin complex concentrates.
Risk factors and risk groups	Possible risk factors include: • History of atherosclerotic disease, coronary artery disease, cerebrovascular disease, crush injury, septicemia, or thromboembolism. • History of congenital and acquired hemophilia receiving concomitant treatment with aPCC/PCC (activated or non-activated prothrombin complex) or other hemostatic agents
Risk minimisation measures	SmPC section 4.4 PL sections 2 & 4
Additional pharmacovigilance activities	Collaboration with EUHASS and PedNet patient registries

Immunogenicity	
Evidence for linking the risk to the medicine	In clinical trials of patients with factor VII deficiency, formation of antibodies against NovoSeven and FVII has been reported. Development of inhibitory antibodies to NovoSeven has been reported in a post-marketing observational registry of patients with congenital FVII deficiency [*Novoseven EU PI*]. In post-marketing experience, there have been no reports of inhibitory antibodies against NovoSeven or FVII in patients with haemophilia A or B [*Novoseven EU PI*].
Risk factors and risk groups	As no case of neutralizing antibodies was observed during clinical development with eptacog beta (activated), no risk factor could be suggested.
Risk minimisation measures	SmPC section 4.4 PL sections 2 & 4
Additional pharmacovigilance activities	Collaboration with EUHASS and PedNet patient registries

Patients with hepatic or renal impairment	
Risk minimisation measures	SmPC section 4.4 PL section 2
Additional pharmacovigilance activities	Collaboration with EUHASS and PedNet patient registries

Elderly patients	
Risk minimisation measures	SmPC section 4.4 PL section 2
Additional pharmacovigilance activities	Collaboration with EUHASS registry

Pregnant and breastfeeding women	
Risk minimisation measures	SmPC section 4.6 PL sections 2
Additional pharmacovigilance activities	Collaboration with EUHASS registry

This is acceptable.

VII. USER CONSULTATION

A full colour mock-up of the Patient Information Leaflet (PIL) has been provided with the application, in accordance with legal requirements.

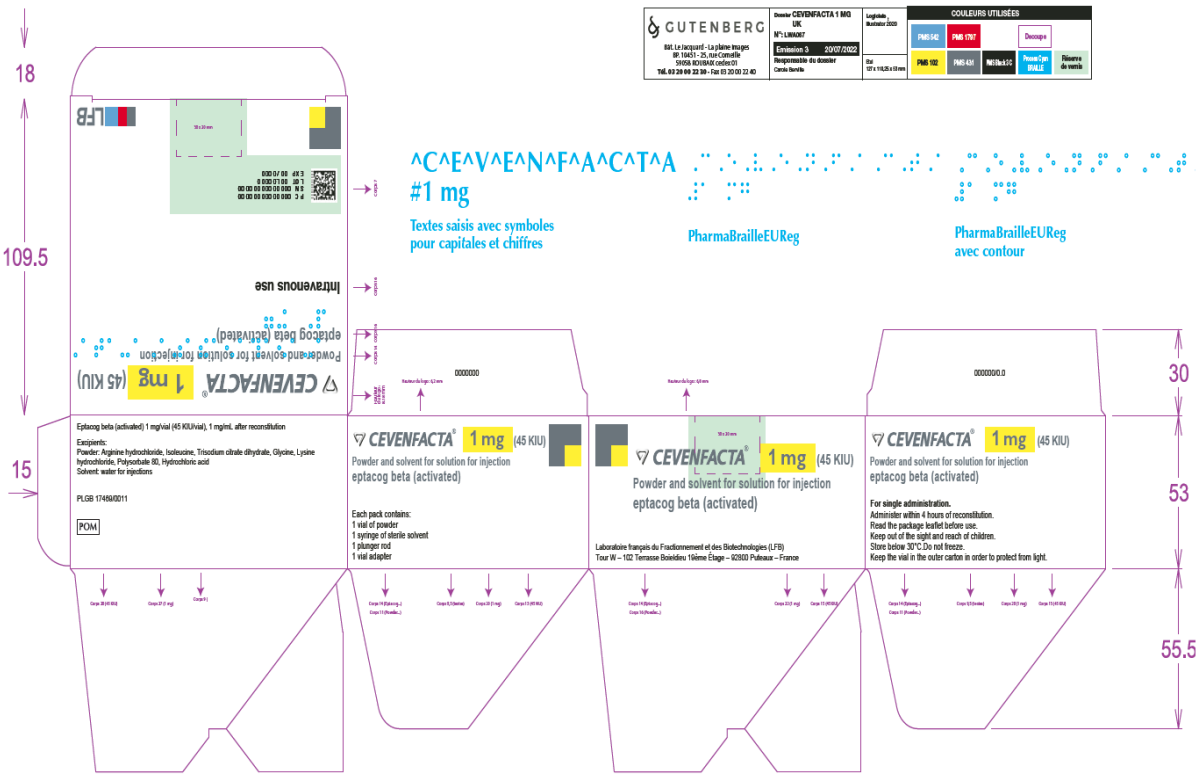
The PIL has been evaluated via a user consultation study in accordance with legal requirements. The results show that the PIL meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

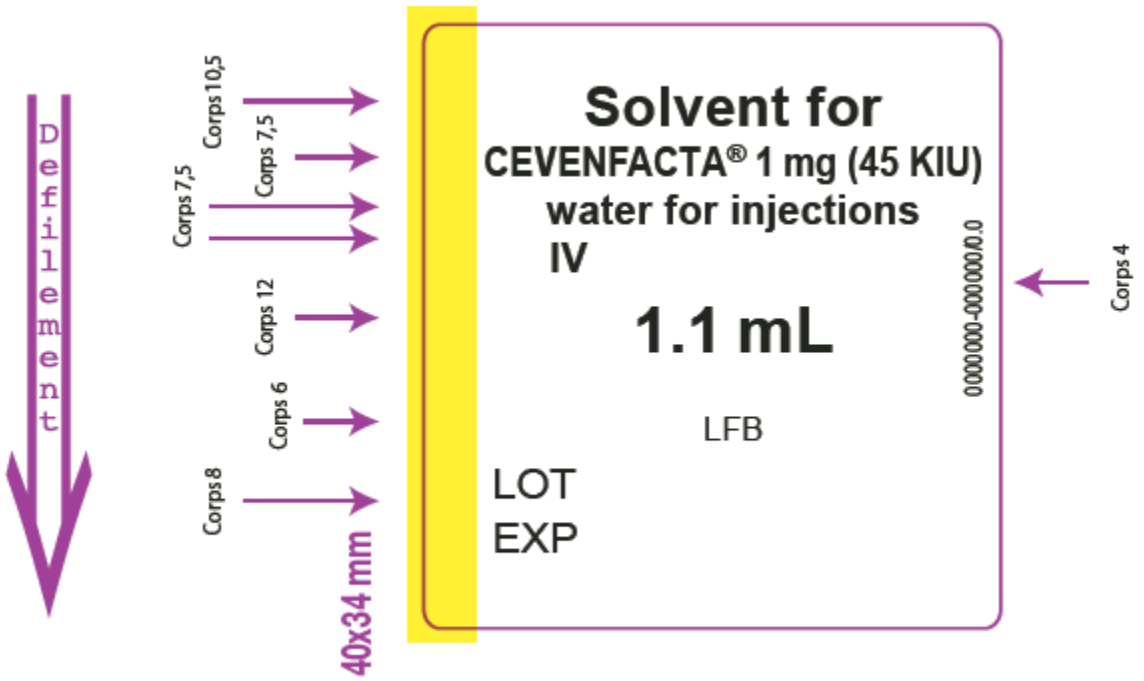
VIII. OVERALL CONCLUSION, BENEFIT/RISK AND RECOMMENDATION

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The benefit/risk balance is, therefore, considered to be positive.
The Summaries of Product Characteristics (SmPCs), Patient Information Leaflet (PIL) and labelling are satisfactory.

In accordance with legal requirements, the current approved UK versions of the SmPCs and PIL for these products are available on the MHRA website.

Representative copies of the labels at the time of UK licensing are provided below.





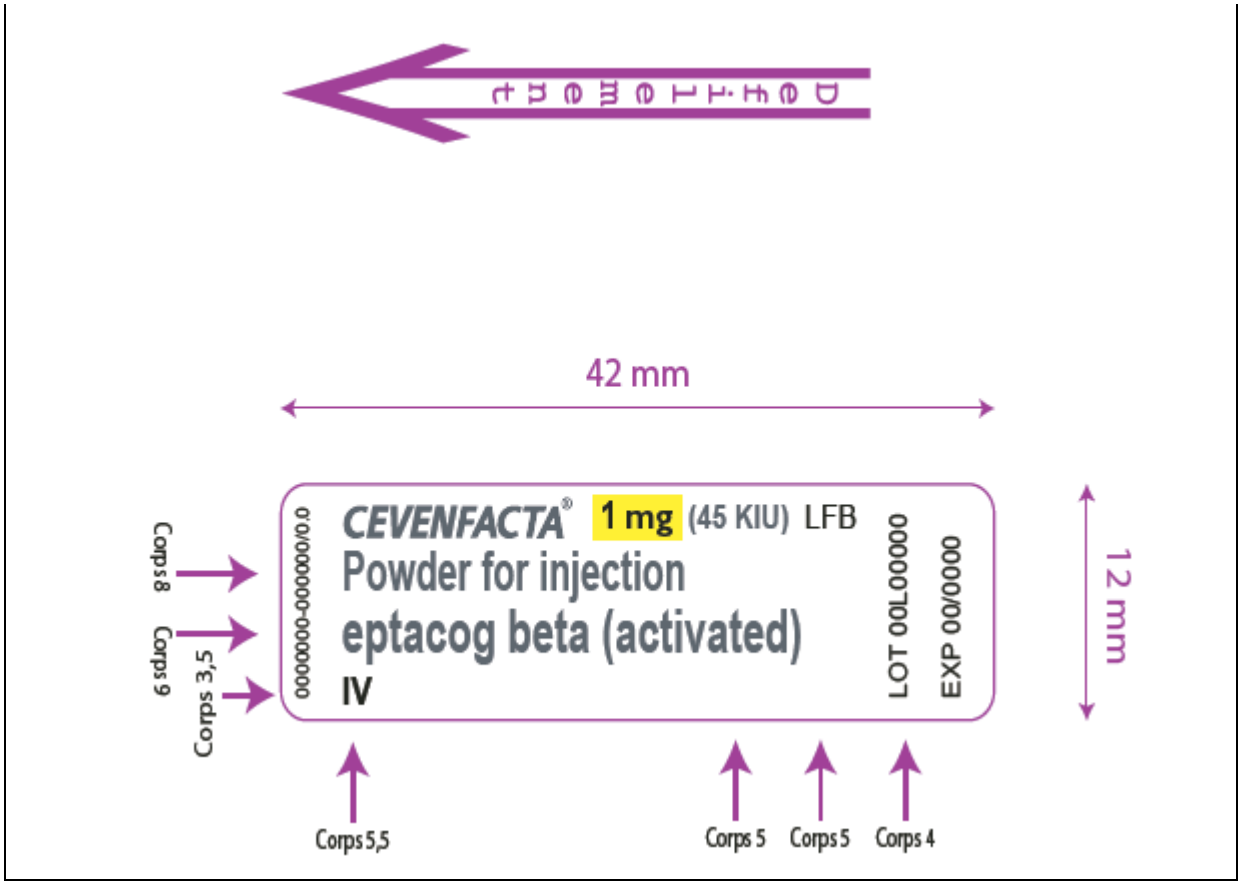

42 mm
CEVENFACTA®
1 mg
(45 KIU) LFB
Powder for injection
eptacog beta (activated)
IV
0000000-000000/0.0
LOT 00L00000
EXP 00/0000
12 mm
Corps 8
Corps 9
Corps 3,5
Corps 5,5
Corps 5
Corps 5
Corps 4

TABLE OF CONTENT OF THE PAR UPDATE

Steps taken after the initial procedure with an influence on the Public Assessment Report (non-safety variations of clinical significance).

Please note that only non-safety variations of clinical significance are recorded below and in the annexes to this PAR. The assessment of safety variations, where significant changes are made, are recorded on the MHRA website or European Medicines Agency (EMA) website. Minor changes to the marketing authorisation are recorded in the current SmPCs and/or PIL available on the MHRA website.

Application type	**Scope**	**Product information affected**	**Date of grant**	**Outcome**	**Assessment report attached Y/N**