Recofact® VII

Recombinant blood coagulation factor VIIa

{Eptacog alfa [activated]}

FORMS AND PRESENTATION
Recofact® VII: lyophilizate for solution for intravenous injections.
COMPOSITION
Recofact® VII 1.2 mg: each vial of the preparation contains:
Active substance: Eptacog alfa [activated] – 1.2mg (60KUI).
Excipients: sodium chloride, calcium chloride dihydrate, glycylglycine, polysorbate-80, mannitol.
• 1 vial with diluents contains: water for injections 5 ml.
• After reconstitution the product contains 0.6 mg/ml eptacog alfa (activated).
PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic group: Blood coagulation factors. ATC code: B02BD08.
Production method
The active drug substance Eptacog alfa - a recombinant blood coagulation factor VIIa with the molecular weight about 50 000 Dalton, produced by genetic engineering from baby hamster kidney cell (BHK cell)
Mechanism of action
Recofact® VII contains activated recombinant coagulation factor VII. The mechanism of action includes the binding of factor VIIa to exposed tissue factor. This complex activates factor IX into factor IXa and factor X into factor Xa, leading to the initial conversion of small amounts of prothrombin into thrombin. Thrombin leads to the activation of platelets and factors V and VIII at the site of injury and to the formation of the haemostatic plug by converting fibrinogen into fibrin. Pharmacological doses of Recofact® VII activate factor X directly on the surface of activated platelets, localized to the site of injury, independently of tissue factor. This results in the conversion of prothrombin into large amounts of thrombin independently of tissue factor.
Pharmacodynamic effect
The pharmacodynamic effect of factor VIIa gives rise to an increased local formation of factor Xa, thrombin and fibrin.
A theoretical risk for the development of systemic activation of the coagulation system in patients suffering from underlying diseases predisposing them to DIC cannot be totally excluded.
In an observational registry focusing on subjects with congenital FVII deficiency, 21 patients (from whom 14 were below 18 years old) were treated with rFVIIa for prophylaxis (24 courses). The frequent administrations of rFVIIa (three times weekly) at a total weekly dose of 90 µg/kg were found to be effective for prophylaxis in FVII deficient patients. No thrombosis nor antibody formation were reported in this registry.
Pharmacokinetic properties
The pharmacokinetics of rFVIIa lyophilizate was investigated in a study on 9 adult patients with hereditary hemophilia in the inhibitory form without bleeding symptoms.
Distribution, elimination and linearity
Mean volume of distribution at steady state was 20.8L.
Mean clearance was 4.0 L/h and mean half-life was 10.0 hours.
The direct dose-dependent relation between the FVII level and the rFVIIa lyophilizate dose was established in patients with hereditary hemophilia in the inhibitory form with hemorrhagic syndrome for the investigated doses of 90 µg/kg – 120 µg/kg.
Pharmacokinetics of rFVIIa lyophilizate in special population was not studied.
INDICATIONS
Recofact® VII is indicated 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 inhibitors to coagulation factors VIII or IX > 5 Bethesda Units (BU)
• in patients with congenital haemophilia who are expected to have a high anamnestic response to factor VIII or factor IX administration
• in patients with acquired haemophilia
• in patients with congenital FVII deficiency
• in patients with Glanzmann's thrombasthenia with antibodies to GP IIb – IIIa and/or HLA, and with past or present refractoriness to platelet transfusions.
CONTRAINDICATIONS
Hypersensitivity to the active substance or to any of the excipients listed or to the mouse, hamster or bovine protein.
PRECAUTIONS
In pathological conditions in which tissue factor may be expressed more extensively than considered normal, there may be a potential risk of development of thrombotic events or induction of Disseminated Intravascular Coagulation (DIC) in association with Recofact® VII treatment.
Such situations may include patients with advanced atherosclerotic disease, crush injury, septicaemia or DIC. Because of the risk of thromboembolic complications, caution should be exercised when administering Recofact® VII to patients with a history of coronary heart disease, to patients with liver disease, to patients post-operatively, to neonates, or to patients at risk of thromboembolic phenomena or disseminated intravascular coagulation. In each of these situations, the potential benefit of treatment with Recofact® VII should be weighed against the risk of these complications.
As recombinant coagulation factor VIIa, Recofact® VII may contain trace amounts of mouse IgG, bovine IgG and other residual culture proteins (hamster and bovine serum proteins), the remote possibility exists that patients treated with the product may develop hypersensitivity to these proteins. In such cases treatment with antihistamines i.v. should be considered.
If allergic or anaphylactic-type reactions occur, the administration should be discontinued immediately. In case of shock, standard medical treatment for shock should be implemented. Patients should be informed of the early signs of hypersensitivity reactions. If such symptoms occur, the patient should be advised to discontinue use of the product immediately and contact their physician.
In case of severe bleeds the product should be administered in hospitals preferably specialized in treatment of haemophilia patients with coagulation factor VIII or IX inhibitors, or if not possible, in close collaboration with a physician specialized in haemophilia treatment.
If bleeding is not kept under control hospital care is mandatory. Patients/carers should inform the physician/supervising hospital at the earliest possible opportunity about all usages of Recofact® VII.
Factor VII deficient patients should be monitored for prothrombin time and factor VII coagulant activity before and after administration of Recofact® VII. In case the factor VIIa activity fails to reach the expected level or bleeding is not controlled after treatment with the recommended doses, antibody formation may be suspected and analysis for antibodies should be performed. Thrombosis has been reported in FVII deficient patients receiving rFVIIa.
Recofact® VII contains less than 1 mmol sodium per vial, i. e. essentially “sodium-free”.

Effects on ability to drive and use machines
No studies on the effect on the ability to drive and use machines have been performed.
FERTILITY, PREGNANCY AND LACTATION
Pregnancy
As a precautionary measure, it is preferable to avoid use of Recofact® VII during pregnancy. Data on a limited number of exposed pregnancies within approved indications indicate no adverse effects of rFVIIa on pregnancy or on the health of the foetus/new-born child. To date, no other relevant epidemiological data are available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/foetal development, parturition or postnatal development.
Breast-feeding
It is unknown whether rFVIIa is excreted in human breast milk. The excretion of rFVIIa in milk has not been studied in animals. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with Recofact® VII should be made taking into account the benefit of breast-feeding to the child and the benefit of Recofact® VII therapy to the woman.
Fertility
Data from non-clinical studies as well as post-marketing data show no indication that rFVIIa has a harmful effect on male or female fertility.
DRUG INTERACTIONS
The risk of a potential interaction between Recofact® VII and coagulation factor concentrates is unknown. Simultaneous use of prothrombin complex concentrates, activated or not, should be avoided.
Anti-fibrinolytics have been reported to reduce blood loss in association with surgery in hemophilia patients, especially in orthopaedic surgery and surgery in regions rich in fibrinolytic activity, such as the oral cavity. Experience with concomitant administration of anti-fibrinolytics and rFVIIa is however limited.
Based on a non-clinical study, it is not recommended to combine rFVIIa and rFXIII.
There are no clinical data available on interaction between rFVIIa and rFXIII.
ADVERSE EFFECTS
The most frequently reported adverse drug reactions are decreased therapeutic response, pyrexia, rash, venous thromboembolic events, pruritus and urticaria. These reactions are reported as uncommon (≥ 1/1000 < 1/100).
The frequencies of both serious and non-serious adverse drug reactions are listed by system organ classes below.
• Blood and lymphatic system disorders: Disseminated intravascular coagulation, Related laboratory findings, including elevated levels of D-dimmer and decreased levels of AT, Coagulopathy (rare).
• Gastrointestinal disorders: Nausea (rare).
• General disorders and administration site conditions: Therapeutic response decreased*, Pyrexia (uncommon); Injection site reaction including injection site pain (rare).
• Immune system disorders: Hypersensitivity (rare); Anaphylactic reaction (not known).
• Investigations: Increased fibrin degradation products, Increase of alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase and prothrombin (rare).
• Nervous system disorders: Headache (rare).
• Skin and subcutaneous tissue disorders: Rash (including allergic dermatitis and rash erythematous), Pruritus and urticarial (uncommon); Flushing, Angioedema (not known).
• Vascular disorders: Venous thromboembolic events (deep vein thrombosis, thrombosis at I.V. site, pulmonary embolism, thromboembolic events of the liver including portal vein thrombosis, renal vein thrombosis, thrombophlebitis, superficial thrombophlebitis and intestinal ischaemia) (uncommon); Arterial thromboembolic events (myocardial infarction, cerebral infarction, cerebral ischaemia, cerebral artery occlusion, cerebrovascular accident, renal artery thrombosis, peripheral ischaemia, peripheral arterial thrombosis and intestinal ischaemia), Angina pectoris (rare); Intracardiac thrombus (not known).
• Respiratory, thoracic and mediastinal disorder: Shortness of breath (not known).
** Lack of efficacy (therapeutic response decreased) has been reported. It is important that the dosage regimen of Recofact® VII is compliant with the recommended dosage as stated in **“DOSAGE AND ADMINISTRATION”***
Description of selected adverse reactions
Inhibitory antibody formation
In post-marketing experience, there have been no reports of inhibitory antibodies against rFVIIa in patients with hemophilia A or B but published data mention the development of inhibitory antibodies to rFVIIa in patients with congenital FVII deficiency. Patients with factor VII deficiency treated with Recofact® VII should be monitored for factor VII antibodies.
Thromboembolic events - arterial and venous
When rFVIIa is administered to patients outside approved indications, arterial thromboembolic events might occur. Published data show that there is a higher risk of arterial thromboembolic adverse events in patients treated with rFVIIa outside current approved indications.
Safety and efficacy of Recofact® VII have not been established outside the approved indications and therefore Recofact® VII should not be used.
Thromboembolic events may lead to cardiac arrest.
Other special populations
Patients with acquired hemophilia
An observational registry focusing on patients with acquired hemophilia A with a total of 174 patients treated with rFVIIa, showed that thrombotic events were reported in 2.9% of these patients (5/174). In only one case, the causal relationship between the treatment and the event (myocardial infarction) was reported by the local investigator. In this case, the thrombotic event was suspected to be related to rFVIIa. In the other cases, the data available in the registry did not allow to assess the causal relationship between the treatment and the thrombotic event.
DOSAGE AND ADMINISTRATION
Treatment should be initiated under the supervision of a physician experienced in the treatment of hemophilia and/or bleeding disorders.
Hemophilia A or B with inhibitors or expected to have a high anamnestic response
Dose
Recofact® VII should be given as early as possible after the start of a bleeding episode. The recommended initial dose, administered by intravenous bolus injection, is 90 µg/kg body weight. Following the initial dose of Recofact® VII further injections may be repeated. The duration of treatment and the interval between injections will vary with the severity of the hemorrhage, the invasive procedures or surgery being performed.
Pediatric population
Current clinical experience does not warrant a general differentiation in dosing between children and adults, although children have faster clearance than adults. Therefore, higher doses of rFVIIa may be needed in pediatric patients to achieve similar plasma concentrations as in adult patients.

Dose interval
Initially 2 – 3 hours to obtain hemostasis.
If continued therapy is needed, the dose interval can be increased successively once effective hemostasis is achieved to every 4, 6, 8 or 12 hours for as long as treatment is judged as being indicated.
Mild to moderate bleeding episodes (including home therapy)
Early intervention has been shown to be efficacious in the treatment of mild to moderate joint, muscle and mucocutaneous bleeds. Two dosing regimens can be recommended:
1) Two to three injections of 90 µg per kg body weight administered at three-hour intervals.
If further treatment is required, one additional dose of 90 µg per kg body weight can be administered.
2) One single injection of 270 µg per kg body weight.
The duration of home therapy should not exceed 24 hours. Only after consultation, home treatment can be considered.
There is no clinical experience with administration of a single dose of 270 µg per kg body weight in elderly patients.
Serious bleeding episodes
An initial dose of 90 µg / kg body weight is recommended and could be administered on the way to the hospital where the patient is usually treated. The following dose varies according to the type and severity of the hemorrhage. The drug is administered each two hours until the bleeding stops. If continued therapy is indicated, the dose interval can then be increased to 3 hours for 1 – 2 days. Thereafter, the dose interval can be increased successively to every 4, 6, 8 or 12 hours for as long as treatment is judged as being indicated. A major bleeding episode may be treated for 2 – 3 weeks but can be extended beyond this if clinically warranted.
Invasive procedure/surgery
An initial dose of 90 µg / kg body weight should be given immediately before the intervention. The dose should be repeated after 2 hours and then at 2 – 3 hour intervals for the first 24 – 48 hours depending on the intervention performed and the clinical status of the patient. In major surgery, the dose should be continued at 2 – 4 hour intervals for 6 – 7 days. The dose interval may then be increased to 6 – 8 hours for another 2 weeks of treatment. Patients undergoing major surgery may be treated for up to 2 – 3 weeks until healing has occurred.

Acquired Hemophilia

Dose and dose interval
Recofact® VII should be given as early as possible after the start of a bleeding episode. The recommended initial dose, administered by intravenous bolus injection, is 90 µg per kg body weight. Following the initial dose of Recofact® VII further injections may be given if required. The duration of treatment and the interval between injections will vary with the severity of the hemorrhage, the invasive procedures or the surgery being performed.
The initial dose interval should be 2 – 3 hours. Once hemostasis has been achieved, the dose interval can be increased successively to every 4, 6, 8 or 12 hours for as long as treatment is judged to be indicated.

Factor VII deficiency

Dose, dose range and dose interval
The recommended dose range in adults and children for treatment of bleeding episodes and for the prevention of bleeding in patients undergoing surgery or invasive procedures is 15 – 30 µg/kg body weight every 4 – 6 hours until hemostasis is achieved. Dose and frequency of injections should be adapted to each individual.
Pediatric population
Limited clinical experience in long term prophylaxis has been gathered in the pediatric population below 12 years of age, with a severe clinical phenotype.
Dose and frequency of inject ions for prophylaxis should be based on clinical response and adapted to each individual.

Glanzmann's thrombasthenia

Dose, dose range and dose interval
The recommended dose for treatment of bleeding episodes and for the prevention of bleeding in patients undergoing surgery or invasive procedures is 90 µg (range 80 – 120 µg) per kg body weight at intervals of two hours (1.5 – 2.5 hours). At least three doses should be administered to secure effective hemostasis.
For those patients who are not refractory, platelets is the first line treatment for Glanzmann's thrombasthenia.

Method of administration

For instructions on reconstitution of the medicinal product before administration, see section **"RECONSTITUTION"**.
Administer the solution as an intravenous bolus injection over 2 – 5 minutes.
Monitoring of treatment – laboratory tests
There is no requirement for monitoring of Recofact® VII therapy. Severity of bleeding condition and clinical response to Recofact® VII administration must guide dosing requirements.
After administration of Recofact® VII, prothrombin time (PT) and activated partial thromboplastin time (aPTT) have been shown to shorten, however no correlation has been demonstrated between PT and aPTT and clinical efficacy of rFVIIa.

OVERDOSAGE

Dose limiting toxicities of Recofact® VII have not been investigated in clinical trials.
The development of antibodies against rFVIIa and FVII has been associated with overdose in one patient with factor VII deficiency.
The dose schedule should not be intentionally increased above the recommended doses due to the absence of information on the additional risk that may be incurred.

RECONSTITUTION

Always use an aseptic technique.
1. Wash your hands thoroughly before the following procedures. Follow the aseptic rules during the preparation and injections of the solution.
2. Warm vials with the drug and solvent, e.g. by holding them in your hands (not higher than 37° C).
3. Place the vial on the flat surface and remove the protective cap from each vial. If the caps are loose or missing, do not use the vials. Wipe the rubber stopper of the vials with the alcohol wipe and allow drying before use.
4. Prepare the syringe with the needle. Protect the needle end of the syringe, with the protective cap still on it, from contact with your hand or any other surfaces.
5. Remove the protective cap from the needle and draw 2ml of the water for injections:
6. Remove the syringe from the first needle, letting it remain in the rubber stopper of the vial with the diluent. Put the second needle on the syringe, with the protective cap still on the needle. Protect the needle end of the syringe from contact with your hand or any other surfaces. Remove the protective cap from the needle.
7. Pierce the rubber stopper of the vial with the drug with the needle, directing it to the wall of the vial and, slowly pressing the plunger, inject the appropriate volume of the water for injections along the wall of the vial, avoiding any foaming and contact of the needle with the drug solution. «Foaming» appears if the water jet strikes the lyophilizate directly.
8. Gently swirl the vial until all the powder is dissolved. Do not shake the vial as this will cause foaming. Check the solution for visible particles and discolouration. If you notice visible particles and/or discolouration, do not use it.
9. Holding the vial in a slightly tilted down position draw the solution into a syringe, pulling the plunger slowly and gradually. Make sure the prepared solution has been fully drawn into a syringe. Put the syringe away with the needle still in the rubber stopper of the vial, until the further manipulations.
10. Prepare the peripheral vein catheter and the injection filter.
11. Not moving the plunger from its position, disconnect the syringe from the needle, leaving the needle in the rubber stopper of the empty vial. Squeeze the air from the syringe. Put the injection filter on the syringe, having previously removed the blister pack. Make sure the filter does not come into any contact with the surfaces.
12. Remove the protective plug from the catheter tube. Connect the unattached end of the injection filter to the catheter tube, having turned the filter clockwise against stop.
13. Take the protective cap off from the catheter needle. Squeeze the air from the syringe and from the attached system for the intravenous injection and start intravenous bolus injection of the solution during 2-5 minutes.
14. Ensure the safe disposal of all the materials used.

If the injection is postponed for any reason, the vial with the medicinal product solution should be stored at 2 to 8 °C for up to 10 hours without freezing or at under 25 °C for up to 8 hours, provided it was prepared under controlled aseptic conditions.
Do not use any solution after this period expires; it should be disposed of.
If the patient needs a dose of more than one vial, similarly prepare the solution in another vial of lyophilisate using the provided solvent (water for injection), then mix the solutions in a larger syringe (not supplied) and inject according to the normal procedure.

INCOMPATIBILITIES

Recofact® VII must not be mixed with infusion solutions or be given in a drip.

CONTENT OF THE PACK

Each pack contains:
• 1 vial with white amorphous mass lyophilizate for the preparation of the solution for the intravenous injections;
• 1 vial with 5 ml diluent, water for injection;
• 1 blister pack together with the medical consumables:
- 1 x 3 mL single-use, sterile, injection syringe
- 2 needles for the preparation of the solution
- 1 peripheral venous catheter
- 2 alcohol swabs.

STORAGE CONDITIONS

Keep at the temperature from 2 to 8°C. Do not freeze.
Store in original package in order to protect from light.
Keep out of the reach of children.

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Manufactured by
Generium JSC, Russia,
for
Benta S.A.L.,
BPI
Dbayeh Lebanon

This is a medicament
- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous for you
- Follow strictly the doctor's prescription, the method of use, and the instructions of the pharmacist who sold the medicament
- The doctor and the pharmacist are experts in medicine, its benefits and risks
- Do not by yourself interrupt the period of treatment prescribed for you
- Do not repeat the same prescription without consulting your doctor
- Medicament: keep out of reach of children

Council of Arab Health Ministers
Union of Arab Pharmacists

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