Recofact® VIII

{B-Domain Deleted Recombinant Factor VIII (BDD-rFVIII)}

(Moroctocog alfa)

FORMS AND PRESENTATION:
Recofact® VIII: Lyophilizate for intravenous solution preparation 500 IU.

COMPOSITION:
• 1 bottle of the drug contains: Moroctocog alfa - 500 IU
Excipients: sodium chloride, sucrose, histidine, calcium chloride, polysorbate 80.
• 1 bottle of the solvent contains: Sodium chloride injection solution 0.9 %; 5 mL.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Pharmacotherapeutic Group: antihaemorrhagics, blood coagulation factor VIII; ATC Code: B02BD02.
Recofact® VIII contains B-domain deleted recombinant coagulation factor VIII (moroctocog alfa). It is a glycoprotein with an approximate molecular mass of 165,000 Da consisting of 1438 amino acids.
Recofact® VIII has functional characteristics comparable to those of endogenous factor VIII. Factor VIII activity is greatly reduced in patients with haemophilia A, and, therefore, replacement therapy is necessary.
When infused into a haemophiliac patient, factor VIII binds to the von Willebrand factor present in the patient's circulation.
Activated factor VIII acts as a cofactor for activated factor IX, accelerating the conversion of factor X to activated factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin, and a clot is formed. Haemophilia A is a sex-linked hereditary disorder of blood coagulation due to decreased levels of factor VIII:C and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. By replacement therapy, the plasma levels of factor VIII are increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.
Pharmacokinetic properties
Pharmacokinetic properties of Recofact® VIII were assessed in a pharmacokinetic study conducted in previously treated adult patients.
For Recofact® VIII 25 IU/kg:
Mean half-life: 13.47 ± 2.37 hours 12.69 ±1.35 hours for 50 IU/kg.
Average Mean Resident Time (MRT):17.16 ±3.04 hours 17.38 ±2.51 hours for Recofact® VIII 50 IU/kg
Mean clearance: 2.17 ± 0.74 dL/h 2.94 ±1.16 dL/h for Recofact® VIII 50 IU/kg.
For Recofact® VIII 50 IU/kg:
Mean half-life: 12.69 ±1.35 hours.
Average Mean Resident Time (MRT): 17.38 ±2.51 hours.
Mean clearance: 2.94 ±1.16 dL/h.

INDICATIONS
Treatment and prophylaxis of bleeding in patients with hemophilia A (congenital factor VIII deficiency).
Recofact® VIII is appropriate for use in adults and children of all ages, including newborns.
Note: Recofact® VIII contains no Willebrand's factor, so it is not indicated for Willebrand's disease treatment.

CONTRAINDICATIONS
Hypersensitivity to the hamster proteins and intolerance of any component of the drug product.

PRECAUTIONS
As with any intravenous protein product, allergic-type hypersensitivity reactions have been observed. The product contains traces of hamster proteins. Patients should be informed of the early signs of hypersensitivity reactions (including hives, generalized urticaria, tightness of the chest, wheezing, hypotension) and anaphylaxis. If allergic or anaphylactic reactions occur, administration of Recofact® VIII is to be discontinued immediately, and an appropriate treatment must be initiated. In case of shock, the current medical standards for treatment of shock are to be observed. Patients are to be advised to discontinue use of the product and contact their physician or seek immediate emergency care, depending on the type and severity of the reaction, if any of these symptoms occur.
The formation of neutralizing antibodies (inhibitors) to factor VIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against the factor VIII procoagulant activity, which are quantified in Bethesda Units (BUs) per ml of plasma using the Nijmegen modification of the Bethesda assay. The risk of developing inhibitors is correlated to the exposure to factor VIII, this risk being highest within the first 20 exposure days.
Inhibitors have been observed in previously treated patients receiving factor VIII products. Cases of recurrence of inhibitors (low titre) have been observed after switching from one recombinant factor VIII product to another in previously treated patients with more than 100 exposure days who have a history of inhibitor development. Patients treated with recombinant coagulation factor VIII should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests.
Reports of lack of efficacy, mainly in prophylaxis patients, have been observed in a post-marketing surveillance study of BDDrFVIII product. When prescribing Recofact® VIII, it is important to individually titrate and monitor each patient's factor level in order to ensure an adequate therapeutic response.
This medicinal product contains less than 1 mmol sodium per vial, i.e. essentially "sodium-free".

Effect on ability to drive vehicles
No studies on the effects on the ability to drive and use machines have been performed.

PREGNANCY AND LACTATION
Animal reproduction studies have not been conducted with factor VIII. Because of the rare occurrence of haemophilia A in women, experience regarding the use of factor VIII during pregnancy and breastfeeding is not available. Therefore, factor VIII should be used during pregnancy and lactation only if clearly indicated.

DRUG INTERACTIONS
No interaction studies have been performed with Recofact® VIII. No interaction has been identified with rFVIII products.

ADVERSE EFFECTS
Factor VIII inhibition
Adverse reactions based on experience from clinical trials with Recofact® VIII and other BDDrFVIII products are presented below by system organ class. These frequencies have been estimated on a per-patient basis and are described using the following categories: very common (=1/10); common (=1/100 to <1/10); and uncommon (=1/1 000 to <1/100).
Blood and lymphatic disorders
Very common: factor VIII inhibitors production in previously untreated patients (PUPs).
Common: factor VIII inhibitors production in previously treated patients (PTPs).
Immune system disorders
Uncommon: Anaphylactoid reaction
Metabolism and nutrition disorders
Uncommon: anorexia.
Nervous system disorders
Common: headache.
Uncommon: neuropathy, dizziness, somnolence, dysgeusia.
Cardiac disorders
Uncommon: angina pectoris, tachycardia, palpitations.
Vascular disorders
Common: hemorrhage or hematoma.
Uncommon: hypotension, thrombophlebitis, vasodilatation, flushing.
Respiratory, thoracic and mediastinal disorders
Uncommon: dyspnoea, cough.
Gastrointestinal disorders
Very common: vomiting.
Common: nausea.
Uncommon: abdominal pain, diarrhea.
Skin and subcutaneous system disorders
Uncommon: urticaria, pruritis, rash, hyperhidrosis.
Musculoskeletal, connective tissue disorders
Common: arthralgia
Uncommon: myalgia.
General disorders and administration site conditions
Common: asthenia, pyrexia, vascular access complications including permanent venous access catheter complications.
Uncommon: chills/feeling cold, injection site inflammation, injection site reaction, injection site pain.
Investigations
Very common: Lab increase for antibody to CHO protein, lab increase of FVIII antibody
Uncommon: Aspartate aminotransferase increased, alanine aminotransferase increased, blood bilirubin increased, blood creatine phosphokinase increased.
Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, generalized urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed infrequently for BDDrFVIII products, and may in some cases progress to severe anaphylaxis including shock.
Trace amounts of hamster protein may be present in Recofact® VIII. Very rarely, development of antibodies to hamster protein has been observed with BDDrFVIII products, but there were no clinical sequelae.
If any reaction takes place that is thought to be related to the administration of Recofact® VIII, the rate of infusion is to be decreased or the infusion stopped, as dictated by the response of the patient.
Pediatric population
In published clinical trials, the studied pediatric population exhibited a safety profile for BDDrFVIII similar to the safety profile known in adults.

DOSAGE AND ADMINISTRATION
Treatment should be initiated under the supervision of a physician experienced in the treatment of haemophilia A.
Recofact® VIII is administered by intravenous injection over several minutes after reconstitution of the lyophilized powder for injection with sodium chloride 9 mg/ml (0.9%) solution for injection (provided). The rate of administration should be determined by the patient's comfort level.
The dosage and duration of the substitution therapy depend on the severity of the factor VIII deficiency, on the location and extent of bleeding, and on the patient's clinical condition. Doses administered should be titrated to the patient's clinical response. In the presence of an inhibitor, higher doses or appropriate specific treatment may be required.
The number of units of factor VIII administered is expressed in International Units (IUs), which are related to the current WHO standard for factor VIII products. Factor VIII activity in plasma is expressed either as a percentage (relative to normal human plasma) or in International Units (relative to an International Standard for factor VIII in

plasma). One International Unit (IU) of factor VIII activity is equivalent to the quantity of factor VIII in one ml of normal human plasma.
The calculation of the required dosage of factor VIII is based upon the empirical finding that 1 International Unit (IU) of factor VIII per kg body weight raises the plasma factor VIII activity by 2 IU/dl. The required dosage is determined using the following formula:
Required units (IU) = body weight (kg) x desired factor VIII rise (% or *IU/dl) x 0.5 (IU/kg per IU/dl),*
Where, 0.5 IU/kg per IU/dl represents the reciprocal of the incremental recovery generally observed following infusions of factor VIII.
The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case.
In the case of the following hemorrhagic events, the factor VIII activity should not fall below the given plasma levels (in % of normal or in IU/dl) in the corresponding period. The following table can be used to guide dosing in bleeding episodes and surgery:

Table of Recofact® VIII dose calculation at different types of bleeding and surgery

Degree of haemorrhage/ Type of surgical procedure	Factor VIII level required (% or IU/dl)	Frequency of doses (hours)/ Duration of therapy (days)
Haemorrhage		
Early hemarthrosis, muscle bleeding or oral bleeding	20 - 40	Repeat every 12-24 hours. At least 1 day, until the bleeding episodes indicated by pain is resolved or healing is achieved
More expensive hemarthrosis, muscle bleeding or hematoma	30 - 60	Repeat infusion every 12-24 hours during 3-4 days or more until pain syndrome and acute disability relieve
Life threatening haemorrhages	60 - 100	Repeat infusion every 8-24 hours until threat is removed
Surgery		
Minor, including tooth extraction	30 - 60	Every 24 hours, at least 1 day, until healing is achieved
Major	80-100 (pre- and post- operative)	Repeated infusions every 8-24 hours until adequate wound healing, then therapy for at least another 7 days to maintain factor VIII activity of 30 to 60% (IU/dl)

During the course of treatment, appropriate determination of factor VIII levels is advised to gtuide the dose to be administered and the frequency of repeated infusions. In the case of major surgical interventions in particular, precise monitoring of the substitution therapy by means of coagulation analysis (plasma factor VIII activity) is indispensable. Individual patients may vary in their response to factor VIII, achieving different levels of in vivo recovery and demonstrating different half-lives.
For long-term prophylaxis against bleeding in patients with severe haemophilia A, the usual doses are 20 to 40 IU of factor VIII per kg body weight at intervals of 2 to 3 days. In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary.
Patients using factor-VIII replacement therapy are to be monitored for the development of factor VIII inhibitors. If expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, an assay should be performed to determine if factor VIII inhibitors are present. Data from clinical trials indicated that if inhibitors are present at levels less than 5 Bethesda Units (BUs), administration of additional antihaemophilic factor may neutralize the inhibitors. In patients with levels of inhibitor above 5 BU, factor VIII therapy may not be effective and other therapeutic options should be considered. Management of such patients should be directed by physicians with experience in the care of patients with haemophilia.

Use in patients with hepatic and renal impairment
Dosage adjustment for patients with renal or hepatic impairment has not been studied in clinical trials.

Use in pediatrics
The need for an increased dose relative to that used for adults and older children should be anticipated when treating younger children with Recofact® VIII as the half-life of BDDrFVIII products was shown to decrease with age.

Reconstitution and administration
1. Thoroughly wash your hands before the following procedures. Asepsis technique should be used during reconstitution and administration procedures.
2. Use opened medical consumables as soon as possible to minimize the time of their contact with air.
3. Warm vials with drug and solvent e.g. by holding them in your hands (not higher than 37°C).
4. Remove protective plastic cap from each vial.
5. Wipe the rubber stoppers of the vials with the alcohol wipe and allow to dry before use.
6. Open the syringe blister package, by pulling the paper to the center.
7. Open the needle blister package, by pulling the paper to the center.
8. Attach the needle to the syringe without removing protective cap. Assure that the syringe tip does not contact with the hands or other objects.
9. Remove protective cap from the needle.
10. Place the vial with the solvent on a flat surface. Pierce the rubber stopper and draw 4 mL of solvent.
11. Open the blister package of the second needle, by pulling the paper to the center.
12. Remove the needle from the syringe, leaving it in the stopper of the vial with the solvent.
13. Attach the second needle to the syringe with the solvent, without removing protective cap.
Assure that the syringe tip does not enter into contact with the hands or other objects. Remove protective cap from the needle.
14. Pierce the rubber stopper of the vial with the drug. Slowly depress the plunger rod to inject 4 mL of the solvent by the vial wall, avoiding foam formation and contact of the needle with the drug solution. "Foaming" appears if the solvent is injected directly on the drug powder.
15. Carefully rotate the vial until all the substance is dissolved. Do not shake the vial. Ensure that the powder is completely dissolved. In case of particulate matter or opacity, the solution cannot be used.
16. Holding the vial in slightly angular position slowly draw all the solution into the syringe.
Ensure that all prepared solution was drawn into the syringe. Remove the air from the syringe. Put aside empty vial with the syringe and needle inside the stopper before the next manipulation.
17. Open the blister package of peripheral venous catheter.
18. Open the blister package of injection filter, by pulling the paper to the center.
19. Without moving the plunger rod, detach the syringe from the needle, leaving it in the stopper. Attach the injection filter (from an open end) to the syringe after removing the blister package. Ensure that injection filter does not contact with other objects.
20. Remove protective blind plug from the catheter tube. Attach free end of injection filter to the catheter tube, turning over the filter clockwise up to the stop. Ensure that the joint is tight.
21. Open the packages of fixing plaster and sorption sterile wipe and treat the injection site with accompanying alcohol wipe.
22. Remove protective cap from the catheter needle. Remove any air in the attached system for intravenous infusion and start introducing the solution intravenously slowly (over 2-5 minutes), previously fixing the catheter needle on the skin by fixing plaster.
23. When the intravenous injection is complete, carefully remove the needle and apply sorption sterile wipe to the infusion site.
24. Provide safe disposal of all the used materials.

If you use more than one dose of the drug, similarly prepare the solution in the vial from another pack, using the provided solvent, then mix the solutions in a larger syringe and inject according to the normal procedure.
Use the prepared solution immediately after dilution. 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 3 hours without freezing.
Do not use any solution after this period expires; it should be disposed of.

OVERDOSAGE
No case of overdose has been reported with Recofact® VIII.

CONTENT OF THE PACK
Each pack contains:
• 1 vial with lyophilizate for intravenous solution preparation
• 1 vial with 5 mL solvent (sodium chloride injection solution 0.9%)
• 1 blister pack with medical consumables:
- 1 x 5 mL single-use, sterile, injection syringe
- 2 needles for reconstitution
- 1 peripheral venous catheter
- 2 alcohol swabs.

STORAGE CONDITIONS
Store refrigerated (2 to 8°C). DO NOT FREEZE.
The drug may be stored in its original package at ≤ 25°C for not more than 24 hours.
Keep the vial in the outer carton in order to protect from light.

KEEP OUT OF REACH OF CHILDREN.
Do not use after the expiration date STATED ON THE PACKAGE.

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Manufactured by:
Generium JSC, Russia
For Benta S.A.L.,
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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