

PACKAGE LEAFLET: INFORMATION FOR THE USER

Helixate NexGen 250 IU powder and solvent for solution for injection Recombinant coagulation factor VIII (octocog alfa)

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any site effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Helixate NexGen 250 IU is and what it is used for
2. Before you use Helixate NexGen 250 IU
3. How to use Helixate NexGen 250 IU
4. Possible side effects
5. How to store Helixate NexGen 250 IU
6. Further information

1. WHAT Helixate NexGen 250 IU IS AND WHAT IT IS USED FOR

One vial with powder for solution for injection nominally contains 250 IU octocog alfa (IU equals International Units). After reconstitution with the appropriate volume of solvent (water for injections), each vial contains octocog alfa 100 IU/ml.

Pharmacotherapeutic group: blood coagulation factor VIII (ATC-Code B02B D02).

Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency).

This preparation does not contain von Willebrand factor and is therefore not indicated in von Willebrand's disease.

2. BEFORE YOU USE Helixate NexGen 250 IU

Do not use Helixate NexGen 250 IU if you are allergic (hypersensitive) to octocog alfa, to mouse or hamster protein or to any of the other ingredients of Helixate NexGen 250 IU.

If you are unsure about this, ask your doctor.

Take special care with Helixate NexGen 250 IU as there is a rare chance that you may experience an anaphylactic reaction (a severe, sudden allergic reaction). If you experience tightness in the chest, feeling dizzy, feeling sick or faint, or experience dizziness on standing, you may be experiencing an allergic reaction to Helixate NexGen 250 IU. If this occurs, stop administering the product immediately and seek medical advice.

Your doctor may wish to carry out tests to ensure that your current dose of Helixate NexGen 250 IU is sufficient to reach and maintain adequate factor VIII levels.

If your bleeding is not being controlled with Helixate NexGen 250 IU, consult your doctor immediately. You may have developed factor VIII inhibitors and your doctor may wish to carry out tests to confirm this. Factor VIII inhibitors are antibodies in the blood which block the factor VIII you are using. This makes factor VIII less effective in controlling bleeding.

If you have previously developed a factor VIII inhibitor and you switch factor VIII products, you may be at risk of your inhibitor coming back.

Using other medicines

Interactions with other medicines are not known. However, please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding

Based on the rare occurrence of haemophilia A in women, experience regarding the use of Helixate NexGen 250 IU during pregnancy and breast-feeding is not available. Therefore, if you are pregnant or breast-feeding consult your doctor before using this product.

Driving and using machines:

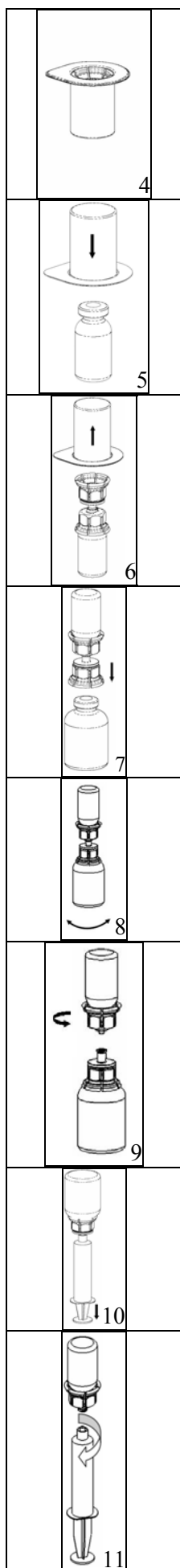
No effects on the ability to drive or use machines have been observed.

Important information about some of the ingredients of Helixate NexGen 250 IU

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially “sodium-free”.

3. HOW TO USE Helixate NexGen 250 IU

Helixate NexGen 250 IU is intended for intravenous administration only and must be administered immediately after reconstitution. Aseptic conditions (meaning clean and germ free) are required during reconstitution and administration. Use only the medical devices for reconstitution and administration provided with each package of Helixate NexGen 250 IU. Helixate NexGen 250 IU must not be mixed with other infusion solutions. Do not use solutions containing visible particles or that are cloudy. Follow the directions given by your doctor closely and use the instructions below as a guide:



1. Wash hands thoroughly using soap and warm water.
2. Warm both unopened vials in your hands to a comfortable temperature (do not exceed 37 °C).
3. Ensure product and diluent vial flip caps are removed and the stoppers are treated with an aseptic solution and allowed to dry prior to opening the Mix2Vial package.
4. Open the Mix2Vial package by peeling away the lid.
5. Place the diluent vial on an even, clean surface and hold the vial tight. Take the Mix2Vial together with the package and snap the blue end onto the diluent stopper.
6. Carefully remove the package from the Mix2Vial set. Make sure that you only pull up the package and not the Mix2Vial set.
7. With the product vial firmly on a surface, invert the diluent vial with set attached and snap the transparent adapter onto the product vial stopper. The diluent will automatically transfer into the product vial.
8. With the diluent and product vial still attached, gently swirl the product vial to ensure the product is fully dissolved. Do not shake vial.
9. With one hand grasp the product-side of the Mix2Vial set and with the other hand grasp the diluent-side of the Mix2Vial set and unscrew the set into two pieces. Draw air (3 ml) into an empty, sterile syringe. While the product vial is upright, connect the syringe to the Mix2Vial set. Inject air into the product vial.
10. While keeping the syringe plunger pressed, invert the system upside down and draw the concentrate into the syringe by pulling the plunger back slowly.
11. Now that the concentrate has been transferred into the syringe, firmly grasp the barrel of the syringe (keeping the syringe plunger facing down) and disconnect the Mix2Vial set from the syringe. Hold the syringe upright and push the plunger until no air is left in the syringe.
12. Apply a tourniquet.
13. Determine the point of injection and prepare antiseptically.
14. Puncture the vein and secure the venipuncture set with a plaster.
15. Let blood flow back to the open end of the venipuncture set and then attach the syringe with the concentrate. Make sure that no blood enters the syringe.
16. Remove tourniquet.
17. Inject the solution intravenously over several minutes, keeping an eye on the position of the needle. The rate of administration should be determined by the patient's comfort (maximum rate of infusion: 2 ml/min).
18. If a further dose needs to be administered, use a new syringe with product reconstituted as described above.
19. If no further dose is required, remove the venipuncture set and syringe. Hold a swab firmly over the injection site on the outstretched arm for approx. 2 minutes. Finally, apply a small pressure dressing to the wound.

The amount of Helixate NexGen 250 IU you should use and how often you use it depends on many factors such as your weight, the severity of your haemophilia, the site and extent of bleeding, the amount of

factor VIII inhibitors that you may have and the factor VIII level required.

Your doctor will calculate the dose of Helixate NexGen 250 IU and how frequently you should use it to get the necessary level of factor VIII activity in your blood. He will do this according to your particular needs using the formulae below.

I.	Required IU = body weight (kg) x desired factor VIII rise (% of normal) x 0.5
II.	Expected factor VIII rise (% of normal) = $\frac{2 \times \text{administered IU}}{\text{body weight (kg)}}$

The following table provides a guide for factor VIII minimum blood levels. In the case of the haemorrhagic events listed, the factor VIII activity should not fall below the given level (in % of normal) in the corresponding period:

Degree of haemorrhage/ Type of surgical procedure	Factor VIII level required (%) (IU/dl)	Frequency of doses (hours)/ Duration of therapy (days)
Haemorrhage		
Early haemarthrosis, muscle bleed or oral bleed	20 - 40	Repeat every 12 to 24 hours. At least 1 day, until the bleeding episode as indicated by pain is resolved or healing is achieved.
More extensive haemarthrosis, muscle bleed or haematoma	30 - 60	Repeat infusion every 12 - 24 hours for 3 - 4 days or more until pain and disability are resolved.
Life threatening bleeds such as intracranial bleed, throat bleed, severe abdominal bleed	60 - 100	Repeat infusion every 8 to 24 hours until threat is resolved
Surgery		
<i>Minor</i> including tooth extraction	30 - 60	Every 24 hours, at least 1 day, until healing is achieved.
<i>Major</i>	80 - 100 (pre- and postoperative)	a) By bolus infusions Repeat infusion every 8 - 24 hours until adequate wound healing occurs, then continue with therapy for at least another 7 days to maintain a factor VIII activity of 30% to 60% b) By continuous infusion Raise factor VIII activity pre-surgery with an initial bolus infusion and immediately follow with continuous infusion (in IU/Kg/h) adjusting according to patient's daily clearance and desired factor VIII levels for at least 7 days.

Your doctor should always adapt the amount of Helixate NexGen 250 IU to be administered and the frequency of administration according to the clinical effectiveness in your individual case. Under certain circumstances larger amounts than those calculated may be required, especially in the case of the initial dose.

If you are using Helixate NexGen 250 IU to prevent bleeding (prophylaxis), your doctor will calculate the dose for you. This will usually be in the range of 20 to 60 IU of octocog alfa per kg of body weight, administered at intervals of 2 to 3 days. However, in some cases, especially younger patients, shorter dose intervals or higher doses may be necessary.

Although dosage can be estimated by the calculations presented above, it is strongly recommended that appropriate laboratory tests be performed on your plasma at suitable intervals to ensure that adequate factor VIII levels have been reached and are maintained. In the case of major surgical interventions in particular, a precise monitoring of the substitution therapy by means of coagulation analysis is indispensable.

If the factor VIII level of your plasma fails to reach expected levels, or if bleeding is not controlled after apparently adequate dosage, the presence of factor VIII inhibitors should be suspected. By appropriate laboratory procedures, the presence of factor VIII inhibitors must be checked and quantified by an experienced doctor.

If you have the impression that the effect of Helixate NexGen 250 IU is too strong or too weak, talk to your doctor.

Patients with inhibitors

If you have been informed by your doctor that you have developed factor VIII inhibitors you will possibly be required to use a larger amount of Helixate NexGen than previously to control a bleeding. If this dose does not control your bleeding your doctor may consider the use of an additional product, factor VIIa concentrate or (activated) prothrombin complex concentrate. Do not increase the dose of Helixate NexGen you use to control your bleeding without consulting your doctor. Speak to your doctor if you would like further information on this.

These therapies should be directed by doctors with experience in the care of patients with haemophilia A.

Helixate NexGen 250 IU should be injected intravenously over several minutes. The rate of administration should be determined by the patient's comfort level (maximal rate of infusion: 2 ml/min).

Your doctor will tell you, how often and at what intervals Helixate NexGen 250 IU is to be administered.

Usually, the substitution therapy with Helixate NexGen 250 IU is a life-time treatment.

If you use more Helixate NexGen 250 IU than you should:

No symptoms of overdose with recombinant coagulation factor VIII have been reported.

If you have used more Helixate NexGen 250 IU than you should, please inform your doctor.

If you forget to use Helixate NexGen 250 IU:

- Proceed with the next administration immediately and continue at regular intervals as advised by your doctor.
- Do not take a double dose to make up for a forgotten doses.

If you stop using Helixate NexGen 250 IU

Do not stop using Helixate NexGen 250 IU without consulting your doctor.

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

4. POSSIBLE SIDE EFFECTS

Like all medicines, Helixate NexGen 250 IU can cause side effects, although not everybody gets them. In rare cases, you may notice any of the following side effects after administration of Helixate NexGen 250 IU:

- rash/itchy rash, local reactions at the injection site (e.g. burning sensation, temporary redness)
- hypersensitivity reactions (e.g. tightness of the chest/general feeling of being unwell, dizziness and nausea and mildly reduced blood pressure, which may make you feel faint upon standing)
- unusual taste in the mouth
- fever.

Furthermore, the possibility of an anaphylactic shock cannot be completely excluded. If you notice any of the following symptoms during injection/infusion:

- chest tightness/general feeling of being unwell
- dizziness
- mild hypotension (mildly reduced blood pressure, which may make you feel faint upon standing)
- nausea

this can constitute an early warning for hypersensitivity and anaphylactic reactions. If allergic or anaphylactic reactions occur, the injection/infusion should be stopped immediately. Please consult your doctor immediately.

During studies, no patient developed clinically relevant antibody titres against the trace amounts of mouse protein and hamster protein present in the preparation. However, the possibility of allergic reactions to constituents, e.g. trace amounts of mouse and hamster protein in the preparation exists in certain predisposed patients.

The formation of neutralising antibodies to factor VIII (inhibitors) is a known complication in the management of individuals with haemophilia A. In studies with recombinant factor VIII preparations, development of inhibitors is predominantly observed in previously untreated haemophiliacs. You should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests.

In clinical studies, Helixate NexGen has been used in the treatment of bleeding episodes in 37 previously untreated patients (PUPs) and 23 minimally treated pediatric patients (MTPs, defined as having equal to or less than 4 exposure days). Five out of 37 (14%) PUP and 4 out of 23 (17%) MTP patients treated with Helixate NexGen developed inhibitors: Overall 6 out of 60 (10%) with a titer above 10 BU and 3 out of 60 (5%) with a titer below 10 BU. The median number of exposure days at the time of inhibitor detection in these patients was 9 days (range 3 - 18 days).

The median number of exposure days in the clinical studies was 114 (range: 4-478). Four of the five patients, who had not achieved 20 exposure days at the end of the study, ultimately achieved more than 20 exposure days in post-study follow-up and one of them developed a low titer inhibitor. The fifth patient was lost to follow-up.

In clinical studies with 73 previously treated patients (PTP, defined as having more than 100 exposure days), followed over four years, no de-novo inhibitors were observed.

In extensive post-registration studies with Helixate NexGen, involving more than 1000 patients the following was observed: Less than 0.2% PTP developed de-novo inhibitors. In a subset defined as having less than 20 exposure days at study entry, less than 11% developed de-novo inhibitors.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE Helixate NexGen 250 IU

Keep out of the reach and sight of children.

Store in a refrigerator (2°C - 8°C). Do not freeze. Keep the vials in the outer carton in order to protect from light.

You may store the product when kept in its outer carton at ambient room temperature (up to 25°C) for a single period of up to 3 months. In this case, the product expires at the end of this 3-month period; you must note the new expiry date on the top of the outer carton.

Do not refrigerate the solution after reconstitution. The reconstituted solution should be used immediately. This product is for single use only. Any unused solution must be discarded.

Do not use Helixate NexGen 250 IU after the expiry date which is stated on labels and cartons. The expiry date refers to the last day of that month.

Do not use Helixate NexGen 250 IU if you notice any particles or the solution is cloudy.

6. FURTHER INFORMATION

What Helixate NexGen 250 IU contains

Powder:

The active substance is recombinant coagulation factor VIII (octocog alfa).

The other ingredients are glycine, sodium chloride, calcium chloride, histidine, polysorbate 80, and sucrose.

Solvent:

Water for injections.

What Helixate NexGen 250 IU looks like and content of the pack

Helixate NexGen 250 IU is provided as a powder and solvent for solution for injection and is a dry white to slightly yellow powder or cake. After reconstitution the solution is clear. Medical devices for reconstitution and administration are provided with each package of Helixate NexGen 250 IU.

Marketing authorisation Holder and Manufacturer

Marketing Authorisation Holder:

Bayer HealthCare AG
D-51368 Leverkusen
Germany

Manufacturer:

Bayer Biologicals S.r.l.
Bellaria, 35
I-53010 Torri-Sovicille (SI)
Italy

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

België / Belgique / Belgien

CSL Behring N.V.
Tél/Tel: +32-(0)16 38 80 80

България

CSL Behring GmbH
Тел. + 49 6421 39 36 54

Česká republika

IBP medica s.r.o.
Tel: +42-02-4143 0299

Danmark

CSL Behring AB
Tlf: +46-(0)8-54496670

Deutschland

CSL Behring GmbH
Tel: +49-(0)69-30584437

Luxembourg / Luxemburg

CSL Behring N.V.
Tél/Tel: +32-(0)16 38 80 80

Magyarország

Plazmed Kft.
Tel: +36-28-59 10 00

Malta

AM Mangion Ltd.
Phone: +356 2397 6000/6412

Nederland

CSL Behring N.V.
Tel: +31-(0)76 523 60 45

Norge

CSL Behring AB
Tlf: +46-(0)8-54496670

Eesti

CSL Behring AB
Tel: +46-(0)8-54496670

Ελλάδα

CSL Behring ΜΕΠΕ,
Τηλ: +30-210 7255 660
+30-210 7255 661

España

CSL Behring, S. A.
Tel: +34 93 367 1870

France

CSL Behring S.A.
Tél: +33-(0)1-53585400

Ireland

CSL Behring UK Limited
Tel: +44-(0)1444 447400

Ísland

CSL Behring AB
Simi: +46-(0)8-54496670

Italia

CSL Behring S.p.A.
Tel: +39-02-349641

Κύπρος

ΑΚΗΣ ΠΑΝΑΓΙΩΤΟΥ & ΥΙΟΣ ΑΤΑ
Τηλ. +357-22677038

Latvija

CSL Behring AB
Tel: +46-(0)8-54496670

Lietuva

CSL Behring AB
Tel. +46-(0)8-54496670

Österreich

CSL Behring GmbH
Tel: +43-(0)1-80101-0

Polska

Imed Poland sp. z.o.o.
Tel. +48 22 663 43 10

Portugal

CSL Behring Lda.
Tel. +351-21-7826230

România

Prisum International Trading srl
Tel. +40 21 250 3688

Slovenija

MediSanus d.o.o.
Tel: +386 1 518 33 97

Slovenská republika

TIMED, s.r.o.
Tel.: +421 2 555 711 82

Suomi/Finland

CSL Behring AB
Puh/Tel: +46-(0)8-54496670

Sverige

CSL Behring AB
Tel: +46-(0)8-54496670

United Kingdom

CSL Behring UK Limited
Tel: +44-(0)1444 447400

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Detailed information on this medicinal product is available on the website of the European Medicines Agency (EMA) <http://www.ema.europa.eu>