ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Helixate NexGen 250 IU powder and solvent for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Each vial contains nominally 250 IU human coagulation factor VIII (INN: octocog alfa).
Human coagulation factor VIII is produced by recombinant DNA technology (rDNA) in baby hamster kidney cells containing the human factor VIII gene.

2.2 Qualitative and quantitative composition

One ml of Helixate NexGen 250 IU contains approximately 100 IU (250 IU / 2.5 ml) of human coagulation factor VIII (INN: octocog alfa) after reconstitution.

The potency (IU) is determined using the one-stage clotting assay against the FDA Mega standard which was calibrated against WHO standard in International Units (IU).
The specific activity of Helixate NexGen is approximately 4000 IU/mg protein.

Solvent: water for injections.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Powder: dry white to slightly yellow powder or cake.
Solvent: water for injection, a clear, colourless solution.

The reconstituted medicinal product is a clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

This product is indicated for adults, adolescents and children of all ages.

4.2 Posology and method of administration

Treatment should be under the supervision of a physician experienced in the treatment of haemophilia.

Posology
The number of units of factor VIII administered is expressed in International Units (IU), 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 the International Standard for factor VIII in plasma).

One International Unit (IU) of factor VIII activity is equivalent to that quantity of factor VIII in one ml of normal human plasma.

On demand treatment

The calculation of the required dose of factor VIII is based on the empirical finding that 1 International Unit (IU) factor VIII per kg body weight raises the plasma factor VIII activity by 1.5% to 2.5% of normal activity. The required dose is determined using the following formulae:

I. Required IU = body weight (kg) × desired factor VIII rise (% of normal) × 0.5

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

The dose, frequency and duration of the substitution therapy must be individualised according to the patient's needs (weight, severity of disorder of the haemostatic function, the site and extent of the bleeding, the presence of inhibitors, and the factor VIII level desired).

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 haemorrhages (such as intracranial bleed, throat bleed, severe abdominal bleed)	60 - 100	Repeat infusion every 8 to 24 hours until threat is resolved
Surgery		
Minor including tooth extraction	30 - 60	Every 24 hours, at least 1 day, until healing is achieved.
Major	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% (IU/dl). 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.

The amount to be administered and the frequency of administration should always be adapted according to the clinical effectiveness in the individual case. Under certain circumstances larger amounts than those calculated may be required, especially in the case of the initial dose.

During the course of treatment, appropriate determination of factor VIII levels is advised in order to guide the dose to be administered and the frequency at which to repeat the 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, demonstrating different half-lives and recoveries.

Continuous Infusion

For the calculation of the initial infusion rate, clearance can be obtained by performing a pre-surgery decay curve, or by starting from an average population value (3.0-3.5 ml/h/kg) and then adjust accordingly.

Infusion rate (in IU/kg/h) = Clearance (in ml/h/kg) × desired factor VIII level (in IU/ml)

For continuous infusion, clinical and *in vitro* stability has been demonstrated using ambulatory pumps with a PVC reservoir. Helixate NexGen contains low level of polysorbate-80 as an excipient, which is known to increase the rate of di-(2-ethylhexyl)phthalate (DEHP) extraction from polyvinyl chloride (PVC) materials. This should be considered for a continuous infusion administration.

Prophylaxis
For long term prophylaxis against bleeding in patients with severe haemophilia A, the usual doses are 20 to 40 IU of Helixate NexGen per kg body weight at intervals of 2 to 3 days.
In some cases, especially in younger patients, shorter dose intervals or higher doses may be necessary.

Paediatric population
The safety and efficacy of Helixate NexGen in children of all ages have been established. Data have been obtained from clinical studies in 61 children under 6 years of age and non-interventional studies in children of all ages.

Patients with inhibitors
Patients should be monitored for the development of factor VIII inhibitors. If the expected plasma factor VIII activity levels are not attained, or if bleeding is not controlled with an appropriate dose, an assay should be performed to determine if a factor VIII inhibitor is present. If the inhibitor is present at levels less than 10 Bethesda Units (BU) per ml, administration of additional recombinant coagulation factor VIII may neutralise the inhibitor and permit continued clinically effective therapy with Helixate NexGen. However, in the presence of an inhibitor the doses required are variable and must be adjusted according to clinical response and monitoring of plasma factor VIII activity. In patients with inhibitor titres above 10 BU or with high anamnestic response, the use of (activated) prothrombin complex concentrate (PCC) or recombinant activated factor VII (rFVIIa) preparations has to be considered. These therapies should be directed by physicians with experience in the care of patients with haemophilia.

Method of administration
Intravenous use.

Helixate NexGen 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).

Continuous infusion
Helixate NexGen can be infused by continuous infusion. The infusion rate should be calculated based on the clearance and the desired FVIII level.
Example: for a 75 kg patient with a clearance of 3 ml/h/kg, the initial infusion rate would be 3 IU/h/kg to achieve a FVIII level of 100%. For calculation of ml/hour, multiply infusion rate in IU/h/kg by kg bw/concentration of solution (IU/ml).

Example for calculation of infusion rate for continuous infusion after initial bolus injection

	Desired plasma FVIII level	Infusion rate IU/h/kg	Infusion rate for 75 kg patient ml/h		
Clearance: 3 ml/h/kg			Concentrations of rFVIII solution 100 IU/ml	200 IU/ml	400 IU/ml
	100 % (1 IU/ml)	3.0	2.25	1.125	0.56
	60 % (0.6 IU/ml)	1.8	1.35	0.68	0.34
	40 % (0.4 IU/ml)	1.2	0.9	0.45	0.225

Higher infusion rates may be required in conditions with accelerated clearance during major bleedings or extensive tissue damage during surgical interventions.

After the initial 24 hours of continuous infusion, the clearance should be recalculated every day using the steady state equation with the measured FVIII level and the rate of infusion using the following equation:
clearance = infusion rate/actual FVIII level.
During continuous infusion, infusion bags should be changed every 24 hours.

For instructions on reconstitution of the medicinal product before administration, see section 6.6 and the package leaflet.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Known allergic reactions to mouse or hamster protein.

4.4 Special warnings and precautions for use

Hypersensitivity
Allergic type hypersensitivity reactions are possible with Helixate NexGen. The product contains traces of mouse and hamster proteins and human proteins other than factor VIII (see section 5.1).

If symptoms of hypersensitivity occur, patients should be advised to discontinue the use of the medicinal product immediately and contact their physician.

Patients should be informed of the early signs of hypersensitivity reactions including hives, nausea, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis.
In case of shock, standard medical treatment for shock should be implemented.

Inhibitors
The formation of neutralising 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 (BU) per ml of plasma using the modified assay. The risk of developing inhibitors is correlated to the exposure to factor VIII and to genetic factors among others, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days.

Cases of recurrence of inhibitors (low titre) have been observed after switching from one factor VIII product to another in previously treated patients with more than 100 exposure days who have a history of inhibitor development. Therefore, it is recommended to monitor all patients carefully for inhibitor occurrence following any product switch.

In general, all patients treated with coagulation factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests.
If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for the presence of factor VIII inhibitor should be performed. In patients with high levels of inhibitor, 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 haemophilia and factor VIII inhibitors.

Continuous infusion
In a clinical study about the use of continuous infusion in surgeries, heparin was used to prevent thrombophlebitis at the infusion site as with any other long term intravenous infusions.

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

Cardiovascular events
Haemophilic patients with cardiovascular risk factors or diseases may be at the same risk to develop cardiovascular events as non-haemophilic patients when clotting has been normalised by treatment with FVIII. Elevation of FVIII levels following administration, in particular with existing cardiovascular risk factors, might put a patient into the same risk for vessel closure or myocardial infarction as for the non-haemophilic population. Consequently, patients should be evaluated and monitored for cardiac risk factors.

Catheter-related complications
If a central venous access device (CVAD) is required, risk of CVAD-related complications including local infections, bacteremia and catheter site thrombosis should be considered.

Documentation
It is strongly recommended that every time that Helixate NexGen is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the medicinal product.

Paediatric population
The listed warnings and precautions apply both to adults and children.

4.5 Interactions with other medicinal products and other forms of interaction

No interactions of Helixate NexGen with other medicinal products have been reported.

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with Helixate NexGen.

Pregnancy and breast-feeding
Based on the rare occurrence of haemophilia A in women, experience regarding the use of Helixate NexGen during pregnancy and breast-feeding is not available. Therefore, Helixate NexGen should be used during pregnancy and breast-feeding only if clearly indicated.

Fertility
There are no fertility data available.

4.7 Effects on ability to drive or use machines

Helixate NexGen has no influence on the ability to drive or to use machines.

4.8 Undesirable effects

Summary of the safety profile
Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed with recombinant factor VIII products and may in some cases progress to severe anaphylaxis (including shock). In particular the skin related reactions may occur commonly, whereas a progress to severe anaphylaxis (including shock) is considered to be rare.

Patients with haemophilia A may develop neutralising antibodies (inhibitors) to factor VIII. The condition may manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted.

Tabulated list of adverse reactions
The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level).

Frequencies have been evaluated according to the following convention: very common: (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

MedDRA Standard System Organ Class	**Frequency**				
	Very common	**Common**	**Uncommon**	**Rare**	**Very Rare / not known**
Blood and the Lymphatic System Disorders	Inhibitor Formation to FVIII (reported in PUPs and MTPs)*		Inhibitor Formation to FVIII (reported in PTPs in clinical trials and Post Marketing Studies)*		
General Disorders and Administration Site Conditions		Infusion site reaction		Infusion related febrile reaction (pyrexia)	
Immune System Disorders		Skin associated hypersensitivity reactions, (pruritus, urticaria and rash)		Systemic Hypersensitivity reactions (including anaphylactic reaction, nausea, blood pressure abnormal and, dizziness)	
Nervous System Disorders					Dysgeusia

PUPs = previously untreated patients
PTPs = previously treated patients
MTPs = minimally treated patients
* see section below

Description of selected adverse reactions
Inhibitor development
Inhibitor development in previously untreated and treated patients (PUPs / PTPs) has been reported (see section 4.4).

In clinical studies, Helixate NexGen has been used in the treatment of bleeding episodes in 37 previously untreated patients (PUPs) and 23 minimally treated paediatric patients (MTPs, defined as having ≤4 exposure days) with residual FVIII:C < 2 IU/dl. Five out of 37 (14%) PUP and 4 out of 23 (17%) MTP patients treated with Helixate NexGen developed inhibitors within 20 exposure days.

Overall, 9 out of 60 (15%) developed inhibitors. One patient was lost to follow up and one patient developed a low-titre inhibitor during post study follow-up.
In one observational study, the incidence of inhibitor development in previously untreated patients with severe haemophilia A was 64/183 (37.7%) with Helixate NexGen (followed up to 75 exposure days).

In clinical studies with 73 previously treated patients (PTP, defined as having ≥100 exposure days), followed over 4 years, no de-novo inhibitors were observed.
In extensive post-registration observational studies with Helixate NexGen, involving more than 1000 patients the following was observed: Less than 0.2% PTP developed de-novo inhibitors.

Paediatric population
Frequency, type and severity of adverse reactions in children are expected to be the same as in all population groups except for the inhibitor formation.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose with recombinant coagulation factor VIII has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihemorrhagics: blood coagulation factor VIII, ATC code B02BD02.

Mechanism of action
The factor VIII/von Willebrand factor (vWF) complex consists of two molecules (factor VIII and vWF) with different physiological functions. When infused into a haemophilic patient, factor VIII binds to vWF 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 can be 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.

Pharmacodynamic effects
Determination of activated partial thromboplastin time (aPTT) is a conventional *in vitro* assay method for biological activity of factor VIII. The aPTT is prolonged in all haemophiliacs. The degree and duration of aPTT normalisation observed after administration of Helixate NexGen is similar to that achieved with plasma-derived factor VIII.

Continuous Infusion
It has been shown in a clinical study performed with adult haemophilia A patients who undergo a major surgery that Helixate NexGen can be used for continuous infusion in surgeries (pre-, during and postoperative). In this study heparin was used to prevent thrombophlebitis at the infusion site as with any other long term intravenous infusions.

Hypersensitivity
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 (see sections 4.3 and 4.4).

Immune Tolerance Induction (ITI)
Data on Immune Tolerance Induction have been collected in patients with haemophilia A who had developed inhibitors to FVIII. A retrospective review has been done on 40 patients, and 39 patients were included in a prospective investigator-initiated clinical study. Data show that Helixate NexGen has been used to induce immune tolerance. In patients where immune tolerance was achieved the bleedings could be prevented or controlled with Helixate NexGen again, and the patients could continue with prophylactic treatment as maintenance therapy.

5.2 Pharmacokinetic properties

Absorption
The analysis of all recorded *in vivo* recoveries in previously treated patients demonstrated a mean rise of 2 % per IU/kg body weight for Helixate NexGen. This result is similar to the reported values for factor VIII derived from human plasma.

Distribution and elimination
After administration of Helixate NexGen, peak factor VIII activity decreased by a two-phase exponential decay with a mean terminal half-life of about 15 hours. This is similar to that of plasma-derived factor VIII which has a mean terminal half-life of approx. 13 hours. Additional pharmacokinetic parameters for Helixate NexGen for bolus injection are: mean residence time [MRT (0-48)] of about 22 hours and clearance of about 160 ml/h.Mean baseline clearance for 14 adult patients undergoing major surgeries with continuous infusion are 188 ml/h corresponding to 3.0 ml/h/kg (range 1.6-4.6 ml/h/kg).

5.3 Preclinical safety data

Even doses several fold higher than the recommended clinical dose (related to body weight) failed to demonstrate any acute or subacute toxic effects for Helixate NexGen in laboratory animals (mouse, rat, rabbit, and dog).

Specific studies with repeated administration such as reproduction toxicity, chronic toxicity, and carcinogenicity were not performed with octocog alfa due to the immune response to heterologous proteins in all non-human mammalian species.

No studies were performed on the mutagenic potential of Helixate NexGen, since no mutagenic potential could be detected *in vitro* or *in vivo* for the predecessor product of Helixate NexGen.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Glycine
Sodium chloride
Calcium chloride
Histidine
Polysorbate 80
Sucrose

Solvent
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.
Only the provided administration sets can be used because treatment failure can occur as a consequence of human recombinant coagulation factor VIII adsorption to the internal surfaces of some infusion equipment.

6.3 Shelf-life

30 months.

After reconstitution, from a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

However, during *in vitro* studies, the chemical and physical in-use stability has been demonstrated for 24 hours at 30°C in PVC bags for continuous infusion". After reconstitution, the chemical and physical in-use stability has been demonstrated for 3 hours in *in vitro* studies.

Do not refrigerate after reconstitution.

6.4 Special precautions for storage

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

Within its overall shelf life of 30 months the product when kept in its outer carton, may be stored at ambient room temperature (up to 25°C) for a limited period of 12 months. In this case, the product expires at the end of this 12-month period or the expiration date on the product vial, whichever is earlier. The new expiry date must be noted on the top of the outer carton.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container and special equipment for use, administration or implantation

Each package of Helixate NexGen contains:
- one vial with powder (10 ml clear glass type 1 vial with latex-free grey halogenobutyl rubber blend stopper and aluminium seal)
- one vial with solvent (6 ml clear glass type 1 vial with latex-free grey chlorobutyl rubber blend stopper and aluminium seal)
- an additional package with:
  - 1 filter transfer device 20/20 [Mix2Vial]
  - 1 venipuncture set
  - 1 disposable 5 ml syringe
  - 2 alcohol swabs for single use

6.6 Special precautions for disposal and other handling

Detailed instructions for preparation and administration are contained in the package leaflet provided with Helixate NexGen.

Helixate NexGen powder should only be reconstituted with the supplied solvent (2.5 ml water for injections) using the supplied sterile Mix2Vial filter transfer device. For infusion, the product must be prepared under aseptic conditions. If any component of the package is opened or damaged, do not use this component.
Gently rotate the vial until all powder is dissolved. After reconstitution the solution is clear.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use Helixate NexGen if you notice visible particulate matter or turbidity.

After reconstitution, the solution is drawn through the Mix2Vial filter transfer device into the sterile disposable syringe (both supplied). Helixate NexGen should be reconstituted and administered with the components provided with each package.

The reconstituted product must be filtered prior to administration to remove potential particulate matter in the solution. Filtering is achieved by using the Mix2Vial adapter.

For single use only. Any unused solution must be discarded.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bayer Pharma AG
13342 Berlin
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/144/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 August 2000
Date of latest renewal: 06 August 2010

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Helixate NexGen 500 IU powder and solvent for solution for injection.

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The potency (IU) is determined using the one-stage clotting assay against the FDA Mega standard which was calibrated against WHO standard in International Units (IU).
The specific activity of Helixate NexGen is approximately 4000 IU/mg protein.

Solvent: water for injections.

For the full list of excipients, see section 6.1.

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Major	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% (IU/dl). 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.

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During the course of treatment, appropriate determination of factor VIII levels is advised in order to guide the dose to be administered and the frequency at which to repeat the 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, demonstrating different half-lives and recoveries.

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Example: for a 75 kg patient with a clearance of 3 ml/h/kg, the initial infusion rate would be 3 IU/h/kg to achieve a FVIII level of 100%. For calculation of ml/hour, multiply infusion rate in IU/h/kg by kg bw/concentration of solution (IU/ml).

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	Desired plasma FVIII level	Infusion rate IU/h/kg	Infusion rate for 75 kg patient ml/h		
Clearance: 3 ml/h/kg			Concentrations of rFVIII solution 100 IU/ml	200 IU/ml	400 IU/ml
	100 % (1 IU/ml)	3.0	2.25	1.125	0.56
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Higher infusion rates may be required in conditions with accelerated clearance during major bleedings or extensive tissue damage during surgical interventions.

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4.4 Special warnings and precautions for use

Hypersensitivity
Allergic type hypersensitivity reactions are possible with Helixate NexGen. The product contains traces of mouse and hamster proteins and human proteins other than factor VIII (see section 5.1).

If symptoms of hypersensitivity occur, patients should be advised to discontinue the use of the medicinal product immediately and contact their physician.

Patients should be informed of the early signs of hypersensitivity reactions including hives, nausea, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis.
In case of shock, standard medical treatment for shock should be implemented.

Inhibitors
The formation of neutralising 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 (BU) per ml of plasma using the modified assay. The risk of developing inhibitors is correlated to the exposure to factor VIII and to genetic factors among others, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days.

Cases of recurrence of inhibitors (low titre) have been observed after switching from one factor VIII product to another in previously treated patients with more than 100 exposure days who have a history of inhibitor development. Therefore, it is recommended to monitor all patients carefully for inhibitor occurrence following any product switch.

In general, all patients treated with coagulation factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests.
If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for the presence of factor VIII inhibitor should be performed. In patients with high levels of inhibitor, 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 haemophilia and factor VIII inhibitors.

Continuous infusion
In a clinical study about the use of continuous infusion in surgeries, heparin was used to prevent thrombophlebitis at the infusion site as with any other long term intravenous infusions.

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

Cardiovascular events
Haemophilic patients with cardiovascular risk factors or diseases may be at the same risk to develop cardiovascular events as non-haemophilic patients when clotting has been normalised by treatment with FVIII. Elevation of FVIII levels following administration, in particular with existing cardiovascular risk factors, might put a patient into the same risk for vessel closure or myocardial infarction as for the non-haemophilic population. Consequently, patients should be evaluated and monitored for cardiac risk factors.

Catheter-related complications
If a central venous access device (CVAD) is required, risk of CVAD-related complications including local infections, bacteremia and catheter site thrombosis should be considered.

Documentation
It is strongly recommended that every time that Helixate NexGen is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the medicinal product.

Paediatric population
The listed warnings and precautions apply both to adults and children.

4.5 Interactions with other medicinal products and other forms of interaction

No interactions of Helixate NexGen with other medicinal products have been reported.

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with Helixate NexGen.

Pregnancy and breast-feeding
Based on the rare occurrence of haemophilia A in women, experience regarding the use of Helixate NexGen during pregnancy and breast-feeding is not available. Therefore, Helixate NexGen should be used during pregnancy and breast-feeding only if clearly indicated.

Fertility
There are no fertility data available.

4.7 Effects on ability to drive or use machines

Helixate NexGen has no influence on the ability to drive or to use machines.

4.8 Undesirable effects

Summary of the safety profile
Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed with recombinant factor VIII products and may in some cases progress to severe anaphylaxis (including shock). In particular the skin related reactions may occur commonly, whereas a progress to severe anaphylaxis (including shock) is considered to be rare.

Patients with haemophilia A may develop neutralising antibodies (inhibitors) to factor VIII. The condition may manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted.

Tabulated list of adverse reactions
The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level).

Frequencies have been evaluated according to the following convention: very common: (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

MedDRA Standard System Organ Class	**Frequency**				
	Very common	**Common**	**Uncommon**	**Rare**	**Very Rare / not known**
Blood and the Lymphatic System Disorders	Inhibitor Formation to FVIII (reported in PUPs and MTPs)*		Inhibitor Formation to FVIII (reported in PTPs in clinical trials and Post Marketing Studies)*		
General Disorders and Administration Site Conditions		Infusion site reaction		Infusion related febrile reaction (pyrexia)	
Immune System Disorders		Skin associated hypersensitivity reactions, (pruritus, urticaria and rash)		Systemic Hypersensitivity reactions (including anaphylactic reaction, nausea, blood pressure abnormal and, dizziness)	
Nervous System Disorders					Dysgeusia

PUPs = previously untreated patients
PTPs = previously treated patients
MTPs = minimally treated patients
* see section below

Description of selected adverse reactions
Inhibitor development
Inhibitor development in previously untreated and treated patients (PUPs / PTPs) has been reported (see section 4.4).

In clinical studies, Helixate NexGen has been used in the treatment of bleeding episodes in 37 previously untreated patients (PUPs) and 23 minimally treated paediatric patients (MTPs, defined as having ≤4 exposure days) with residual FVIII:C < 2 IU/dl. Five out of 37 (14%) PUP and 4 out of 23 (17%) MTP patients treated with Helixate NexGen developed inhibitors within 20 exposure days.

Overall, 9 out of 60 (15%) developed inhibitors. One patient was lost to follow up and one patient developed a low-titre inhibitor during post study follow-up.
In one observational study, the incidence of inhibitor development in previously untreated patients with severe haemophilia A was 64/183 (37.7%) with Helixate NexGen (followed up to 75 exposure days).

In clinical studies with 73 previously treated patients (PTP, defined as having ≥100 exposure days), followed over 4 years, no de-novo inhibitors were observed.
In extensive post-registration observational studies with Helixate NexGen, involving more than 1000 patients the following was observed: Less than 0.2% PTP developed de-novo inhibitors.

Paediatric population
Frequency, type and severity of adverse reactions in children are expected to be the same as in all population groups except for the inhibitor formation.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose with recombinant coagulation factor VIII has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihemorrhagics: blood coagulation factor VIII, ATC code B02BD02.

Mechanism of action
The factor VIII/von Willebrand factor (vWF) complex consists of two molecules (factor VIII and vWF) with different physiological functions. When infused into a haemophilic patient, factor VIII binds to vWF 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 can be 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.

Pharmacodynamic effects
Determination of activated partial thromboplastin time (aPTT) is a conventional *in vitro* assay method for biological activity of factor VIII. The aPTT is prolonged in all haemophiliacs. The degree and duration of aPTT normalisation observed after administration of Helixate NexGen is similar to that achieved with plasma-derived factor VIII.

Continuous Infusion
It has been shown in a clinical study performed with adult haemophilia A patients who undergo a major surgery that Helixate NexGen can be used for continuous infusion in surgeries (pre-, during and postoperative). In this study heparin was used to prevent thrombophlebitis at the infusion site as with any other long term intravenous infusions.

Hypersensitivity
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 (see sections 4.3 and 4.4).

Immune Tolerance Induction (ITI)
Data on Immune Tolerance Induction have been collected in patients with haemophilia A who had developed inhibitors to FVIII. A retrospective review has been done on 40 patients, and 39 patients were included in a prospective investigator-initiated clinical study. Data show that Helixate NexGen has been used to induce immune tolerance. In patients where immune tolerance was achieved the bleedings could be prevented or controlled with Helixate NexGen again, and the patients could continue with prophylactic treatment as maintenance therapy.

5.2 Pharmacokinetic properties

Absorption
The analysis of all recorded *in vivo* recoveries in previously treated patients demonstrated a mean rise of 2 % per IU/kg body weight for Helixate NexGen. This result is similar to the reported values for factor VIII derived from human plasma.

Distribution and elimination
After administration of Helixate NexGen, peak factor VIII activity decreased by a two-phase exponential decay with a mean terminal half-life of about 15 hours. This is similar to that of plasma-derived factor VIII which has a mean terminal half-life of approx. 13 hours. Additional pharmacokinetic parameters for Helixate NexGen for bolus injection are: mean residence time [MRT (0-48)] of about 22 hours and clearance of about 160 ml/h.Mean baseline clearance for 14 adult patients undergoing major surgeries with continuous infusion are 188 ml/h corresponding to 3.0 ml/h/kg (range 1.6-4.6 ml/h/kg).

5.3 Preclinical safety data

Even doses several fold higher than the recommended clinical dose (related to body weight) failed to demonstrate any acute or subacute toxic effects for Helixate NexGen in laboratory animals (mouse, rat, rabbit, and dog).

Specific studies with repeated administration such as reproduction toxicity, chronic toxicity, and carcinogenicity were not performed with octocog alfa due to the immune response to heterologous proteins in all non-human mammalian species.

No studies were performed on the mutagenic potential of Helixate NexGen, since no mutagenic potential could be detected *in vitro* or *in vivo* for the predecessor product of Helixate NexGen.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Glycine
Sodium chloride
Calcium chloride
Histidine
Polysorbate 80
Sucrose

Solvent
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.
Only the provided administration sets can be used because treatment failure can occur as a consequence of human recombinant coagulation factor VIII adsorption to the internal surfaces of some infusion equipment.

6.3 Shelf-life

30 months.

After reconstitution, from a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

However, during *in vitro* studies, the chemical and physical in-use stability has been demonstrated for 24 hours at 30°C in PVC bags for continuous infusion". After reconstitution, the chemical and physical in-use stability has been demonstrated for 3 hours in *in vitro* studies.

Do not refrigerate after reconstitution.

6.4 Special precautions for storage

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

Within its overall shelf life of 30 months the product when kept in its outer carton, may be stored at ambient room temperature (up to 25°C) for a limited period of 12 months. In this case, the product expires at the end of this 12-month period or the expiration date on the product vial, whichever is earlier. The new expiry date must be noted on the top of the outer carton.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container and special equipment for use, administration or implantation

Each package of Helixate NexGen contains:
- one vial with powder (10 ml clear glass type 1 vial with latex-free grey halogenobutyl rubber blend stopper and aluminium seal)
- one vial with solvent (6 ml clear glass type 1 vial with latex-free grey chlorobutyl rubber blend stopper and aluminium seal)
- an additional package with:
  - 1 filter transfer device 20/20 [Mix2Vial]
  - 1 venipuncture set
  - 1 disposable 5 ml syringe
  - 2 alcohol swabs for single use

6.6 Special precautions for disposal and other handling

Detailed instructions for preparation and administration are contained in the package leaflet provided with Helixate NexGen.

Helixate NexGen powder should only be reconstituted with the supplied solvent (2.5 ml water for injections) using the supplied sterile Mix2Vial filter transfer device. For infusion, the product must be prepared under aseptic conditions. If any component of the package is opened or damaged, do not use this component.
Gently rotate the vial until all powder is dissolved. After reconstitution the solution is clear.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use Helixate NexGen if you notice visible particulate matter or turbidity.

After reconstitution, the solution is drawn through the Mix2Vial filter transfer device into the sterile disposable syringe (both supplied). Helixate NexGen should be reconstituted and administered with the components provided with each package.

The reconstituted product must be filtered prior to administration to remove potential particulate matter in the solution. Filtering is achieved by using the Mix2Vial adapter.

For single use only. Any unused solution must be discarded.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bayer Pharma AG
13342 Berlin
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/144/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 August 2000
Date of latest renewal: 06 August 2010

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Helixate NexGen 1000 IU powder and solvent for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Each vial contains nominally 1000 IU human coagulation factor VIII (INN: octocog alfa).
Human coagulation factor VIII is produced by recombinant DNA technology (rDNA) in baby hamster kidney cells containing the human factor VIII gene.

2.2 Qualitative and quantitative composition

One ml of Helixate NexGen 1000 IU contains approximately 400 IU (1000 IU / 2.5 ml) of human coagulation factor VIII (INN: octocog alfa) after reconstitution.

The potency (IU) is determined using the one-stage clotting assay against the FDA Mega standard which was calibrated against WHO standard in International Units (IU).
The specific activity of Helixate NexGen is approximately 4000 IU/mg protein.

Solvent: water for injections.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Powder: dry white to slightly yellow powder or cake.
Solvent: water for injection, a clear, colourless solution.

The reconstituted medicinal product is a clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

This product is indicated for adults, adolescents and children of all ages.

4.2 Posology and method of administration

Treatment should be under the supervision of a physician experienced in the treatment of haemophilia.

Posology
The number of units of factor VIII administered is expressed in International Units (IU), 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 the International Standard for factor VIII in plasma).

One International Unit (IU) of factor VIII activity is equivalent to that quantity of factor VIII in one ml of normal human plasma.

On demand treatment
The calculation of the required dose of factor VIII is based on the empirical finding that 1 International Unit (IU) factor VIII per kg body weight raises the plasma factor VIII activity by 1.5% to 2.5% of normal activity. The required dose is determined using the following formulae:

I. Required IU = body weight (kg) × desired factor VIII rise (% of normal) × 0.5

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

The dose, frequency and duration of the substitution therapy must be individualised according to the patient's needs (weight, severity of disorder of the haemostatic function, the site and extent of the bleeding, the presence of inhibitors, and the factor VIII level desired).

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 haemorrhages (such as intracranial bleed, throat bleed, severe abdominal bleed)	60 - 100	Repeat infusion every 8 to 24 hours until threat is resolved
Surgery *Minor* including tooth extraction	30 - 60	Every 24 hours, at least 1 day, until healing is achieved.
Major	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% (IU/dl). 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.

The amount to be administered and the frequency of administration should always be adapted according to the clinical effectiveness in the individual case. Under certain circumstances larger amounts than those calculated may be required, especially in the case of the initial dose.

During the course of treatment, appropriate determination of factor VIII levels is advised in order to guide the dose to be administered and the frequency at which to repeat the 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, demonstrating different half-lives and recoveries.

Continuous Infusion

For the calculation of the initial infusion rate, clearance can be obtained by performing a pre-surgery decay curve, or by starting from an average population value (3.0-3.5 ml/h/kg) and then adjust accordingly.

Infusion rate (in IU/kg/h) = Clearance (in ml/h/kg) × desired factor VIII level (in IU/ml)

For continuous infusion, clinical and *in vitro* stability has been demonstrated using ambulatory pumps with a PVC reservoir. Helixate NexGen contains low level of polysorbate-80 as an excipient, which is known to increase the rate of di-(2-ethylhexyl)phthalate (DEHP) extraction from polyvinyl chloride (PVC) materials. This should be considered for a continuous infusion administration.

Prophylaxis
For long term prophylaxis against bleeding in patients with severe haemophilia A, the usual doses are 20 to 40 IU of Helixate NexGen per kg body weight at intervals of 2 to 3 days.
In some cases, especially in younger patients, shorter dose intervals or higher doses may be necessary.

Paediatric population
The safety and efficacy of Helixate NexGen in children of all ages have been established. Data have been obtained from clinical studies in 61 children under 6 years of age and non-interventional studies in children of all ages.

Patients with inhibitors
Patients should be monitored for the development of factor VIII inhibitors. If the expected plasma factor VIII activity levels are not attained, or if bleeding is not controlled with an appropriate dose, an assay should be performed to determine if a factor VIII inhibitor is present. If the inhibitor is present at levels less than 10 Bethesda Units (BU) per ml, administration of additional recombinant coagulation factor VIII may neutralise the inhibitor and permit continued clinically effective therapy with Helixate NexGen. However, in the presence of an inhibitor the doses required are variable and must be adjusted according to clinical response and monitoring of plasma factor VIII activity. In patients with inhibitor titres above 10 BU or with high anamnestic response, the use of (activated) prothrombin complex concentrate (PCC) or recombinant activated factor VII (rFVIIa) preparations has to be considered. These therapies should be directed by physicians with experience in the care of patients with haemophilia.

Method of administration
Intravenous use.

Helixate NexGen 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).

Continuous infusion
Helixate NexGen can be infused by continuous infusion. The infusion rate should be calculated based on the clearance and the desired FVIII level.
Example: for a 75 kg patient with a clearance of 3 ml/h/kg, the initial infusion rate would be 3 IU/h/kg to achieve a FVIII level of 100%. For calculation of ml/hour, multiply infusion rate in IU/h/kg by kg bw/concentration of solution (IU/ml).

Example for calculation of infusion rate for continuous infusion after initial bolus injection

	Desired plasma FVIII level	Infusion rate IU/h/kg	Infusion rate for 75 kg patient ml/h		
Clearance: 3 ml/h/kg			Concentrations of rFVIII solution 100 IU/ml	200 IU/ml	400 IU/ml
	100 % (1 IU/ml)	3.0	2.25	1.125	0.56
	60 % (0.6 IU/ml)	1.8	1.35	0.68	0.34
	40 % (0.4 IU/ml)	1.2	0.9	0.45	0.225

Higher infusion rates may be required in conditions with accelerated clearance during major bleedings or extensive tissue damage during surgical interventions.

After the initial 24 hours of continuous infusion, the clearance should be recalculated every day using the steady state equation with the measured FVIII level and the rate of infusion using the following equation:
clearance = infusion rate/actual FVIII level.
During continuous infusion, infusion bags should be changed every 24 hours.

For instructions on reconstitution of the medicinal product before administration, see section 6.6 and the package leaflet.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Known allergic reactions to mouse or hamster protein.

4.4 Special warnings and precautions for use

Hypersensitivity
Allergic type hypersensitivity reactions are possible with Helixate NexGen. The product contains traces of mouse and hamster proteins and human proteins other than factor VIII (see section 5.1).

If symptoms of hypersensitivity occur, patients should be advised to discontinue the use of the medicinal product immediately and contact their physician.

Patients should be informed of the early signs of hypersensitivity reactions including hives, nausea, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis.
In case of shock, standard medical treatment for shock should be implemented.

Inhibitors
The formation of neutralising 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 (BU) per ml of plasma using the modified assay. The risk of developing inhibitors is correlated to the exposure to factor VIII and to genetic factors among others, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days.

Cases of recurrence of inhibitors (low titre) have been observed after switching from one factor VIII product to another in previously treated patients with more than 100 exposure days who have a history of inhibitor development. Therefore, it is recommended to monitor all patients carefully for inhibitor occurrence following any product switch.

In general, all patients treated with coagulation factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests.
If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for the presence of factor VIII inhibitor should be performed. In patients with high levels of inhibitor, 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 haemophilia and factor VIII inhibitors.

Continuous infusion
In a clinical study about the use of continuous infusion in surgeries, heparin was used to prevent thrombophlebitis at the infusion site as with any other long term intravenous infusions.

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

Cardiovascular events
Haemophilic patients with cardiovascular risk factors or diseases may be at the same risk to develop cardiovascular events as non-haemophilic patients when clotting has been normalised by treatment with FVIII. Elevation of FVIII levels following administration, in particular with existing cardiovascular risk factors, might put a patient into the same risk for vessel closure or myocardial infarction as for the non-haemophilic population. Consequently, patients should be evaluated and monitored for cardiac risk factors.

Catheter-related complications
If a central venous access device (CVAD) is required, risk of CVAD-related complications including local infections, bacteremia and catheter site thrombosis should be considered.

Documentation
It is strongly recommended that every time that Helixate NexGen is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the medicinal product.

Paediatric population
The listed warnings and precautions apply both to adults and children.

4.5 Interactions with other medicinal products and other forms of interaction

No interactions of Helixate NexGen with other medicinal products have been reported.

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with Helixate NexGen.

Pregnancy and breast-feeding
Based on the rare occurrence of haemophilia A in women, experience regarding the use of Helixate NexGen during pregnancy and breast-feeding is not available. Therefore, Helixate NexGen should be used during pregnancy and breast-feeding only if clearly indicated.

Fertility
There are no fertility data available.

4.7 Effects on ability to drive or use machines

Helixate NexGen has no influence on the ability to drive or to use machines.

4.8 Undesirable effects

Summary of the safety profile
Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed with recombinant factor VIII products and may in some cases progress to severe anaphylaxis (including shock). In particular the skin related reactions may occur commonly, whereas a progress to severe anaphylaxis (including shock) is considered to be rare.

Patients with haemophilia A may develop neutralising antibodies (inhibitors) to factor VIII. The condition may manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted.

Tabulated list of adverse reactions
The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level).

Frequencies have been evaluated according to the following convention: very common: (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

MedDRA Standard System Organ Class	**Frequency**				
	Very common	**Common**	**Uncommon**	**Rare**	**Very Rare / not known**
Blood and the Lymphatic System Disorders	Inhibitor Formation to FVIII (reported in PUPs and MTPs)*		Inhibitor Formation to FVIII (reported in PTPs in clinical trials and Post Marketing Studies)*		
General Disorders and Administration Site Conditions		Infusion site reaction		Infusion related febrile reaction (pyrexia)	
Immune System Disorders		Skin associated hypersensitivity reactions, (pruritus, urticaria and rash)		Systemic Hypersensitivity reactions (including anaphylactic reaction, nausea, blood pressure abnormal and, dizziness)	
Nervous System Disorders					Dysgeusia

PUPs = previously untreated patients
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MTPs = minimally treated patients
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Description of selected adverse reactions
Inhibitor development
Inhibitor development in previously untreated and treated patients (PUPs / PTPs) has been reported (see section 4.4).

In clinical studies, Helixate NexGen has been used in the treatment of bleeding episodes in 37 previously untreated patients (PUPs) and 23 minimally treated paediatric patients (MTPs, defined as having ≤4 exposure days) with residual FVIII:C < 2 IU/dl. Five out of 37 (14%) PUP and 4 out of 23 (17%) MTP patients treated with Helixate NexGen developed inhibitors within 20 exposure days.

Overall, 9 out of 60 (15%) developed inhibitors. One patient was lost to follow up and one patient developed a low-titre inhibitor during post study follow-up.
In one observational study, the incidence of inhibitor development in previously untreated patients with severe haemophilia A was 64/183 (37.7%) with Helixate NexGen (followed up to 75 exposure days).

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In extensive post-registration observational studies with Helixate NexGen, involving more than 1000 patients the following was observed: Less than 0.2% PTP developed de-novo inhibitors.

Paediatric population
Frequency, type and severity of adverse reactions in children are expected to be the same as in all population groups except for the inhibitor formation.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose with recombinant coagulation factor VIII has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihemorrhagics: blood coagulation factor VIII, ATC code B02BD02.

Mechanism of action
The factor VIII/von Willebrand factor (vWF) complex consists of two molecules (factor VIII and vWF) with different physiological functions. When infused into a haemophilic patient, factor VIII binds to vWF 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 can be 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.

Pharmacodynamic effects
Determination of activated partial thromboplastin time (aPTT) is a conventional *in vitro* assay method for biological activity of factor VIII. The aPTT is prolonged in all haemophiliacs. The degree and duration of aPTT normalisation observed after administration of Helixate NexGen is similar to that achieved with plasma-derived factor VIII.

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It has been shown in a clinical study performed with adult haemophilia A patients who undergo a major surgery that Helixate NexGen can be used for continuous infusion in surgeries (pre-, during and postoperative). In this study heparin was used to prevent thrombophlebitis at the infusion site as with any other long term intravenous infusions.

Hypersensitivity
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 (see sections 4.3 and 4.4).

Immune Tolerance Induction (ITI)
Data on Immune Tolerance Induction have been collected in patients with haemophilia A who had developed inhibitors to FVIII. A retrospective review has been done on 40 patients, and 39 patients were included in a prospective investigator-initiated clinical study. Data show that Helixate NexGen has been used to induce immune tolerance. In patients where immune tolerance was achieved the bleedings could be prevented or controlled with Helixate NexGen again, and the patients could continue with prophylactic treatment as maintenance therapy.

5.2 Pharmacokinetic properties

Absorption
The analysis of all recorded *in vivo* recoveries in previously treated patients demonstrated a mean rise of 2 % per IU/kg body weight for Helixate NexGen. This result is similar to the reported values for factor VIII derived from human plasma.

Distribution and elimination
After administration of Helixate NexGen, peak factor VIII activity decreased by a two-phase exponential decay with a mean terminal half-life of about 15 hours. This is similar to that of plasma-derived factor VIII which has a mean terminal half-life of approx. 13 hours. Additional pharmacokinetic parameters for Helixate NexGen for bolus injection are: mean residence time [MRT (0-48)] of about 22 hours and clearance of about 160 ml/h.Mean baseline clearance for 14 adult patients undergoing major surgeries with continuous infusion are 188 ml/h corresponding to 3.0 ml/h/kg (range 1.6-4.6 ml/h/kg).

5.3 Preclinical safety data

Even doses several fold higher than the recommended clinical dose (related to body weight) failed to demonstrate any acute or subacute toxic effects for Helixate NexGen in laboratory animals (mouse, rat, rabbit, and dog).

Specific studies with repeated administration such as reproduction toxicity, chronic toxicity, and carcinogenicity were not performed with octocog alfa due to the immune response to heterologous proteins in all non-human mammalian species.

No studies were performed on the mutagenic potential of Helixate NexGen, since no mutagenic potential could be detected *in vitro* or *in vivo* for the predecessor product of Helixate NexGen.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Glycine
Sodium chloride
Calcium chloride
Histidine
Polysorbate 80
Sucrose

Solvent
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.
Only the provided administration sets can be used because treatment failure can occur as a consequence of human recombinant coagulation factor VIII adsorption to the internal surfaces of some infusion equipment.

6.3 Shelf-life

30 months.

After reconstitution, from a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

However, during *in vitro* studies, the chemical and physical in-use stability has been demonstrated for 24 hours at 30°C in PVC bags for continuous infusion". After reconstitution, the chemical and physical in-use stability has been demonstrated for 3 hours in *in vitro* studies.

Do not refrigerate after reconstitution.

6.4 Special precautions for storage

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

Within its overall shelf life of 30 months the product when kept in its outer carton, may be stored at ambient room temperature (up to 25°C) for a limited period of 12 months. In this case, the product expires at the end of this 12-month period or the expiration date on the product vial, whichever is earlier. The new expiry date must be noted on the top of the outer carton.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container and special equipment for use, administration or implantation

Each package of Helixate NexGen contains:
- one vial with powder (10 ml clear glass type 1 vial with latex-free grey halogenobutyl rubber blend stopper and aluminium seal)
- one vial with solvent (6 ml clear glass type 1 vial with latex-free grey chlorobutyl rubber blend stopper and aluminium seal)
- an additional package with:
  - 1 filter transfer device 20/20 [Mix2Vial]
  - 1 venipuncture set
  - 1 disposable 5 ml syringe
  - 2 alcohol swabs for single use

6.6 Special precautions for disposal and other handling

Detailed instructions for preparation and administration are contained in the package leaflet provided with Helixate NexGen.

Helixate NexGen powder should only be reconstituted with the supplied solvent (2.5 ml water for injections) using the supplied sterile Mix2Vial filter transfer device. For infusion, the product must be prepared under aseptic conditions. If any component of the package is opened or damaged, do not use this component.
Gently rotate the vial until all powder is dissolved. After reconstitution the solution is clear.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use Helixate NexGen if you notice visible particulate matter or turbidity.

After reconstitution, the solution is drawn through the Mix2Vial filter transfer device into the sterile disposable syringe (both supplied). Helixate NexGen should be reconstituted and administered with the components provided with each package.

The reconstituted product must be filtered prior to administration to remove potential particulate matter in the solution. Filtering is achieved by using the Mix2Vial adapter.

For single use only. Any unused solution must be discarded.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bayer Pharma AG
13342 Berlin
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/144/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 August 2000
Date of latest renewal: 06 August 2010

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Helixate NexGen 2000 IU powder and solvent for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Each vial contains nominally 2000 IU human coagulation factor VIII (INN: octocog alfa).
Human coagulation factor VIII is produced by recombinant DNA technology (rDNA) in baby hamster kidney cells containing the human factor VIII gene.

2.2 Qualitative and quantitative composition

One ml of Helixate NexGen 2000 IU contains approximately 400 IU (2000 IU / 5.0 ml) of human coagulation factor VIII (INN: octocog alfa) after reconstitution.

The potency (IU) is determined using the one-stage clotting assay against the FDA Mega standard which was calibrated against WHO standard in International Units (IU).
The specific activity of Helixate NexGen is approximately 4000 IU/mg protein.

Solvent: water for injections.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Powder: dry white to slightly yellow powder or cake.
Solvent: water for injection, a clear, colourless solution.

The reconstituted medicinal product is a clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

This product is indicated for adults, adolescents and children of all ages.

4.2 Posology and method of administration

Treatment should be under the supervision of a physician experienced in the treatment of haemophilia.

Posology
The number of units of factor VIII administered is expressed in International Units (IU), 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 the International Standard for factor VIII in plasma).

One International Unit (IU) of factor VIII activity is equivalent to that quantity of factor VIII in one ml of normal human plasma.

On demand treatment
The calculation of the required dose of factor VIII is based on the empirical finding that 1 International Unit (IU) factor VIII per kg body weight raises the plasma factor VIII activity by 1.5% to 2.5% of normal activity. The required dose is determined using the following formulae:

I. Required IU = body weight (kg) × desired factor VIII rise (% of normal) × 0.5

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

The dose, frequency and duration of the substitution therapy must be individualised according to the patient's needs (weight, severity of disorder of the haemostatic function, the site and extent of the bleeding, the presence of inhibitors, and the factor VIII level desired).

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 haemorrhages (such as intracranial bleed, throat bleed, severe abdominal bleed)	60 - 100	Repeat infusion every 8 to 24 hours until threat is resolved
Surgery *Minor* including tooth extraction	30 - 60	Every 24 hours, at least 1 day, until healing is achieved.
Major	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% (IU/dl). 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.

The amount to be administered and the frequency of administration should always be adapted according to the clinical effectiveness in the individual case. Under certain circumstances larger amounts than those calculated may be required, especially in the case of the initial dose.

During the course of treatment, appropriate determination of factor VIII levels is advised in order to guide the dose to be administered and the frequency at which to repeat the 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, demonstrating different half-lives and recoveries.

Continuous Infusion

For the calculation of the initial infusion rate, clearance can be obtained by performing a pre-surgery decay curve, or by starting from an average population value (3.0-3.5 ml/h/kg) and then adjust accordingly.

Infusion rate (in IU/kg/h) = Clearance (in ml/h/kg) × desired factor VIII level (in IU/ml)

For continuous infusion, clinical and *in vitro* stability has been demonstrated using ambulatory pumps with a PVC reservoir. Helixate NexGen contains low level of polysorbate-80 as an excipient, which is known to increase the rate of di-(2-ethylhexyl)phthalate (DEHP) extraction from polyvinyl chloride (PVC) materials. This should be considered for a continuous infusion administration.

Prophylaxis
For long term prophylaxis against bleeding in patients with severe haemophilia A, the usual doses are 20 to 40 IU of Helixate NexGen per kg body weight at intervals of 2 to 3 days.
In some cases, especially in younger patients, shorter dose intervals or higher doses may be necessary.

Paediatric population
The safety and efficacy of Helixate NexGen in children of all ages have been established. Data have been obtained from clinical studies in 61 children under 6 years of age and non-interventional studies in children of all ages.

Patients with inhibitors
Patients should be monitored for the development of factor VIII inhibitors. If the expected plasma factor VIII activity levels are not attained, or if bleeding is not controlled with an appropriate dose, an assay should be performed to determine if a factor VIII inhibitor is present. If the inhibitor is present at levels less than 10 Bethesda Units (BU) per ml, administration of additional recombinant coagulation factor VIII may neutralise the inhibitor and permit continued clinically effective therapy with Helixate NexGen. However, in the presence of an inhibitor the doses required are variable and must be adjusted according to clinical response and monitoring of plasma factor VIII activity. In patients with inhibitor titres above 10 BU or with high anamnestic response, the use of (activated) prothrombin complex concentrate (PCC) or recombinant activated factor VII (rFVIIa) preparations has to be considered. These therapies should be directed by physicians with experience in the care of patients with haemophilia.

Method of administration
Intravenous use.

Helixate NexGen 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).

Continuous infusion
Helixate NexGen can be infused by continuous infusion. The infusion rate should be calculated based on the clearance and the desired FVIII level.
Example: for a 75 kg patient with a clearance of 3 ml/h/kg, the initial infusion rate would be 3 IU/h/kg to achieve a FVIII level of 100%. For calculation of ml/hour, multiply infusion rate in IU/h/kg by kg bw/concentration of solution (IU/ml).

Example for calculation of infusion rate for continuous infusion after initial bolus injection

	Desired plasma FVIII level	Infusion rate IU/h/kg	Infusion rate for 75 kg patient ml/h		
Clearance: 3 ml/h/kg			Concentrations of rFVIII solution 100 IU/ml	200 IU/ml	400 IU/ml
	100 % (1 IU/ml)	3.0	2.25	1.125	0.56
	60 % (0.6 IU/ml)	1.8	1.35	0.68	0.34
	40 % (0.4 IU/ml)	1.2	0.9	0.45	0.225

Higher infusion rates may be required in conditions with accelerated clearance during major bleedings or extensive tissue damage during surgical interventions.

After the initial 24 hours of continuous infusion, the clearance should be recalculated every day using the steady state equation with the measured FVIII level and the rate of infusion using the following equation:
clearance = infusion rate/actual FVIII level.
During continuous infusion, infusion bags should be changed every 24 hours.

For instructions on reconstitution of the medicinal product before administration, see section 6.6 and the package leaflet.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Known allergic reactions to mouse or hamster protein.

4.4 Special warnings and precautions for use

Hypersensitivity
Allergic type hypersensitivity reactions are possible with Helixate NexGen. The product contains traces of mouse and hamster proteins and human proteins other than factor VIII (see section 5.1).

If symptoms of hypersensitivity occur, patients should be advised to discontinue the use of the medicinal product immediately and contact their physician.

Patients should be informed of the early signs of hypersensitivity reactions including hives, nausea, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis.
In case of shock, standard medical treatment for shock should be implemented.

Inhibitors
The formation of neutralising 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 (BU) per ml of plasma using the modified assay. The risk of developing inhibitors is correlated to the exposure to factor VIII and to genetic factors among others, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days.

Cases of recurrence of inhibitors (low titre) have been observed after switching from one factor VIII product to another in previously treated patients with more than 100 exposure days who have a history of inhibitor development. Therefore, it is recommended to monitor all patients carefully for inhibitor occurrence following any product switch.

In general, all patients treated with coagulation factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests.
If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for the presence of factor VIII inhibitor should be performed. In patients with high levels of inhibitor, 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 haemophilia and factor VIII inhibitors.

Continuous infusion
In a clinical study about the use of continuous infusion in surgeries, heparin was used to prevent thrombophlebitis at the infusion site as with any other long term intravenous infusions.

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

Cardiovascular events
Haemophilic patients with cardiovascular risk factors or diseases may be at the same risk to develop cardiovascular events as non-haemophilic patients when clotting has been normalised by treatment with FVIII. Elevation of FVIII levels following administration, in particular with existing cardiovascular risk factors, might put a patient into the same risk for vessel closure or myocardial infarction as for the non-haemophilic population. Consequently, patients should be evaluated and monitored for cardiac risk factors.

Catheter-related complications
If a central venous access device (CVAD) is required, risk of CVAD-related complications including local infections, bacteremia and catheter site thrombosis should be considered.

Documentation
It is strongly recommended that every time that Helixate NexGen is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the medicinal product.

Paediatric population
The listed warnings and precautions apply both to adults and children.

4.5 Interactions with other medicinal products and other forms of interaction

No interactions of Helixate NexGen with other medicinal products have been reported.

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with Helixate NexGen.

Pregnancy and breast-feeding
Based on the rare occurrence of haemophilia A in women, experience regarding the use of Helixate NexGen during pregnancy and breast-feeding is not available. Therefore, Helixate NexGen should be used during pregnancy and breast-feeding only if clearly indicated.

Fertility
There are no fertility data available.

4.7 Effects on ability to drive or use machines

Helixate NexGen has no influence on the ability to drive or to use machines.

4.8 Undesirable effects

Summary of the safety profile
Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed with recombinant factor VIII products and may in some cases progress to severe anaphylaxis (including shock). In particular the skin related reactions may occur commonly, whereas a progress to severe anaphylaxis (including shock) is considered to be rare.

Patients with haemophilia A may develop neutralising antibodies (inhibitors) to factor VIII. The condition may manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted.

Tabulated list of adverse reactions
The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level).

Frequencies have been evaluated according to the following convention: very common: (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

MedDRA Standard System Organ Class	**Frequency**				
	Very common	**Common**	**Uncommon**	**Rare**	**Very Rare / not known**
Blood and the Lymphatic System Disorders	Inhibitor Formation to FVIII (reported in PUPs and MTPs)*		Inhibitor Formation to FVIII (reported in PTPs in clinical trials and Post Marketing Studies)*		
General Disorders and Administration Site Conditions		Infusion site reaction		Infusion related febrile reaction (pyrexia)	
Immune System Disorders		Skin associated hypersensitivity reactions, (pruritus, urticaria and rash)		Systemic Hypersensitivity reactions (including anaphylactic reaction, nausea, blood pressure abnormal and, dizziness)	
Nervous System Disorders					Dysgeusia

PUPs = previously untreated patients
PTPs = previously treated patients
MTPs = minimally treated patients
* see section below

Description of selected adverse reactions
Inhibitor development
Inhibitor development in previously untreated and treated patients (PUPs / PTPs) has been reported (see section 4.4).

In clinical studies, Helixate NexGen has been used in the treatment of bleeding episodes in 37 previously untreated patients (PUPs) and 23 minimally treated paediatric patients (MTPs, defined as having ≤4 exposure days) with residual FVIII:C < 2 IU/dl. Five out of 37 (14%) PUP and 4 out of 23 (17%) MTP patients treated with Helixate NexGen developed inhibitors within 20 exposure days.

Overall, 9 out of 60 (15%) developed inhibitors. One patient was lost to follow up and one patient developed a low-titre inhibitor during post study follow-up.
In one observational study, the incidence of inhibitor development in previously untreated patients with severe haemophilia A was 64/183 (37.7%) with Helixate NexGen (followed up to 75 exposure days).

In clinical studies with 73 previously treated patients (PTP, defined as having ≥100 exposure days), followed over 4 years, no de-novo inhibitors were observed.
In extensive post-registration observational studies with Helixate NexGen, involving more than 1000 patients the following was observed: Less than 0.2% PTP developed de-novo inhibitors.

Paediatric population
Frequency, type and severity of adverse reactions in children are expected to be the same as in all population groups except for the inhibitor formation.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose with recombinant coagulation factor VIII has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihemorrhagics: blood coagulation factor VIII, ATC code B02BD02.

Mechanism of action
The factor VIII/von Willebrand factor (vWF) complex consists of two molecules (factor VIII and vWF) with different physiological functions. When infused into a haemophilic patient, factor VIII binds to vWF 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 can be 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.

Pharmacodynamic effects
Determination of activated partial thromboplastin time (aPTT) is a conventional *in vitro* assay method for biological activity of factor VIII. The aPTT is prolonged in all haemophiliacs. The degree and duration of aPTT normalisation observed after administration of Helixate NexGen is similar to that achieved with plasma-derived factor VIII.

Continuous Infusion
It has been shown in a clinical study performed with adult haemophilia A patients who undergo a major surgery that Helixate NexGen can be used for continuous infusion in surgeries (pre-, during and postoperative). In this study heparin was used to prevent thrombophlebitis at the infusion site as with any other long term intravenous infusions.

Hypersensitivity
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 (see sections 4.3 and 4.4).

Immune Tolerance Induction (ITI)
Data on Immune Tolerance Induction have been collected in patients with haemophilia A who had developed inhibitors to FVIII. A retrospective review has been done on 40 patients, and 39 patients were included in a prospective investigator-initiated clinical study. Data show that Helixate NexGen has been used to induce immune tolerance. In patients where immune tolerance was achieved the bleedings could be prevented or controlled with Helixate NexGen again, and the patients could continue with prophylactic treatment as maintenance therapy.

5.2 Pharmacokinetic properties

Absorption
The analysis of all recorded *in vivo* recoveries in previously treated patients demonstrated a mean rise of 2 % per IU/kg body weight for Helixate NexGen. This result is similar to the reported values for factor VIII derived from human plasma.

Distribution and elimination
After administration of Helixate NexGen, peak factor VIII activity decreased by a two-phase exponential decay with a mean terminal half-life of about 15 hours. This is similar to that of plasma-derived factor VIII which has a mean terminal half-life of approx. 13 hours. Additional pharmacokinetic parameters for Helixate NexGen for bolus injection are: mean residence time [MRT (0-48)] of about 22 hours and clearance of about 160 ml/h.Mean baseline clearance for 14 adult patients undergoing major surgeries with continuous infusion are 188 ml/h corresponding to 3.0 ml/h/kg (range 1.6-4.6 ml/h/kg).

5.3 Preclinical safety data

Even doses several fold higher than the recommended clinical dose (related to body weight) failed to demonstrate any acute or subacute toxic effects for Helixate NexGen in laboratory animals (mouse, rat, rabbit, and dog).

Specific studies with repeated administration such as reproduction toxicity, chronic toxicity, and carcinogenicity were not performed with octocog alfa due to the immune response to heterologous proteins in all non-human mammalian species.

No studies were performed on the mutagenic potential of Helixate NexGen, since no mutagenic potential could be detected *in vitro* or *in vivo* for the predecessor product of Helixate NexGen.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Glycine
Sodium chloride
Calcium chloride
Histidine
Polysorbate 80
Sucrose

Solvent
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.
Only the provided administration sets can be used because treatment failure can occur as a consequence of human recombinant coagulation factor VIII adsorption to the internal surfaces of some infusion equipment.

6.3 Shelf-life

30 months.

After reconstitution, from a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

However, during *in vitro* studies, the chemical and physical in-use stability has been demonstrated for 24 hours at 30°C in PVC bags for continuous infusion". After reconstitution, the chemical and physical in-use stability has been demonstrated for 3 hours in *in vitro* studies.

Do not refrigerate after reconstitution.

6.4 Special precautions for storage

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

Within its overall shelf life of 30 months the product when kept in its outer carton, may be stored at ambient room temperature (up to 25°C) for a limited period of 12 months. In this case, the product expires at the end of this 12-month period or the expiration date on the product vial, whichever is earlier. The new expiry date must be noted on the top of the outer carton.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container and special equipment for use, administration or implantation

Each package of Helixate NexGen contains:
- one vial with powder (10 ml clear glass type 1 vial with latex-free grey halogenobutyl rubber blend stopper and aluminium seal)
- one vial with solvent (6 ml clear glass type 1 vial with latex-free grey chlorobutyl rubber blend stopper and aluminium seal)
- an additional package with:
  - 1 filter transfer device 20/20 [Mix2Vial]
  - 1 venipuncture set
  - 1 disposable 5 ml syringe
  - 2 alcohol swabs for single use

6.6 Special precautions for disposal and other handling

Detailed instructions for preparation and administration are contained in the package leaflet provided with Helixate NexGen.

Helixate NexGen powder should only be reconstituted with the supplied solvent (5.0 ml water for injections) using the supplied sterile Mix2Vial filter transfer device. For infusion, the product must be prepared under aseptic conditions. If any component of the package is opened or damaged, do not use this component.
Gently rotate the vial until all powder is dissolved. After reconstitution the solution is clear.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use Helixate NexGen if you notice visible particulate matter or turbidity.

After reconstitution, the solution is drawn through the Mix2Vial filter transfer device into the sterile disposable syringe (both supplied). Helixate NexGen should be reconstituted and administered with the components provided with each package.

The reconstituted product must be filtered prior to administration to remove potential particulate matter in the solution. Filtering is achieved by using the Mix2Vial adapter.

For single use only. Any unused solution must be discarded.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bayer Pharma AG
13342 Berlin
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/144/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 August 2000
Date of latest renewal: 06 August 2010

10. DATE OF REVISION OF THE TEXT

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

1. NAME OF THE MEDICINAL PRODUCT

Helixate NexGen 3000 IU powder and solvent for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Each vial contains nominally 3000 IU human coagulation factor VIII (INN: octocog alfa).
Human coagulation factor VIII is produced by recombinant DNA technology (rDNA) in baby hamster kidney cells containing the human factor VIII gene.

2.2 Qualitative and quantitative composition

One ml of Helixate NexGen 3000 IU contains approximately 600 IU (3000 IU / 5.0 ml) of human coagulation factor VIII (INN: octocog alfa) after reconstitution.

The potency (IU) is determined using the one-stage clotting assay against the FDA Mega standard which was calibrated against WHO standard in International Units (IU).
The specific activity of Helixate NexGen is approximately 4000 IU/mg protein.

Solvent: water for injections.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

Powder: dry white to slightly yellow powder or cake.
Solvent: water for injection, a clear, colourless solution.

The reconstituted medicinal product is a clear and colourless solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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.

This product is indicated for adults, adolescents and children of all ages.

4.2 Posology and method of administration

Treatment should be under the supervision of a physician experienced in the treatment of haemophilia.

Posology
The number of units of factor VIII administered is expressed in International Units (IU), 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 the International Standard for factor VIII in plasma).

One International Unit (IU) of factor VIII activity is equivalent to that quantity of factor VIII in one ml of normal human plasma.

On demand treatment
The calculation of the required dose of factor VIII is based on the empirical finding that 1 International Unit (IU) factor VIII per kg body weight raises the plasma factor VIII activity by 1.5% to 2.5% of normal activity. The required dose is determined using the following formulae:

I. Required IU = body weight (kg) × desired factor VIII rise (% of normal) × 0.5

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

The dose, frequency and duration of the substitution therapy must be individualised according to the patient's needs (weight, severity of disorder of the haemostatic function, the site and extent of the bleeding, the presence of inhibitors, and the factor VIII level desired).

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 haemorrhages (such as intracranial bleed, throat bleed, severe abdominal bleed)	60 - 100	Repeat infusion every 8 to 24 hours until threat is resolved
Surgery *Minor* including tooth extraction	30 - 60	Every 24 hours, at least 1 day, until healing is achieved.
Major	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% (IU/dl). 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.

The amount to be administered and the frequency of administration should always be adapted according to the clinical effectiveness in the individual case. Under certain circumstances larger amounts than those calculated may be required, especially in the case of the initial dose.

During the course of treatment, appropriate determination of factor VIII levels is advised in order to guide the dose to be administered and the frequency at which to repeat the 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, demonstrating different half-lives and recoveries.

Continuous Infusion

For the calculation of the initial infusion rate, clearance can be obtained by performing a pre-surgery decay curve, or by starting from an average population value (3.0-3.5 ml/h/kg) and then adjust accordingly.

Infusion rate (in IU/kg/h) = Clearance (in ml/h/kg) × desired factor VIII level (in IU/ml)

For continuous infusion, clinical and *in vitro* stability has been demonstrated using ambulatory pumps with a PVC reservoir. Helixate NexGen contains low level of polysorbate-80 as an excipient, which is known to increase the rate of di-(2-ethylhexyl)phthalate (DEHP) extraction from polyvinyl chloride (PVC) materials. This should be considered for a continuous infusion administration.

Prophylaxis
For long term prophylaxis against bleeding in patients with severe haemophilia A, the usual doses are 20 to 40 IU of Helixate NexGen per kg body weight at intervals of 2 to 3 days.
In some cases, especially in younger patients, shorter dose intervals or higher doses may be necessary.

Paediatric population
The safety and efficacy of Helixate NexGen in children of all ages have been established. Data have been obtained from clinical studies in 61 children under 6 years of age and non-interventional studies in children of all ages.

Patients with inhibitors
Patients should be monitored for the development of factor VIII inhibitors. If the expected plasma factor VIII activity levels are not attained, or if bleeding is not controlled with an appropriate dose, an assay should be performed to determine if a factor VIII inhibitor is present. If the inhibitor is present at levels less than 10 Bethesda Units (BU) per ml, administration of additional recombinant coagulation factor VIII may neutralise the inhibitor and permit continued clinically effective therapy with Helixate NexGen. However, in the presence of an inhibitor the doses required are variable and must be adjusted according to clinical response and monitoring of plasma factor VIII activity. In patients with inhibitor titres above 10 BU or with high anamnestic response, the use of (activated) prothrombin complex concentrate (PCC) or recombinant activated factor VII (rFVIIa) preparations has to be considered. These therapies should be directed by physicians with experience in the care of patients with haemophilia.

Method of administration
Intravenous use.

Helixate NexGen 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).

Continuous infusion
Helixate NexGen can be infused by continuous infusion. The infusion rate should be calculated based on the clearance and the desired FVIII level.
Example: for a 75 kg patient with a clearance of 3 ml/h/kg, the initial infusion rate would be 3 IU/h/kg to achieve a FVIII level of 100%. For calculation of ml/hour, multiply infusion rate in IU/h/kg by kg bw/concentration of solution (IU/ml).

Example for calculation of infusion rate for continuous infusion after initial bolus injection

	Desired plasma FVIII level	Infusion rate IU/h/kg	Infusion rate for 75 kg patient ml/h		
Clearance: 3 ml/h/kg			Concentrations of rFVIII solution 100 IU/ml	200 IU/ml	400 IU/ml
	100 % (1 IU/ml)	3.0	2.25	1.125	0.56
	60 % (0.6 IU/ml)	1.8	1.35	0.68	0.34
	40 % (0.4 IU/ml)	1.2	0.9	0.45	0.225

Higher infusion rates may be required in conditions with accelerated clearance during major bleedings or extensive tissue damage during surgical interventions.

After the initial 24 hours of continuous infusion, the clearance should be recalculated every day using the steady state equation with the measured FVIII level and the rate of infusion using the following equation:
clearance = infusion rate/actual FVIII level.
During continuous infusion, infusion bags should be changed every 24 hours.

For instructions on reconstitution of the medicinal product before administration, see section 6.6 and the package leaflet.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Known allergic reactions to mouse or hamster protein.

4.4 Special warnings and precautions for use

Hypersensitivity
Allergic type hypersensitivity reactions are possible with Helixate NexGen. The product contains traces of mouse and hamster proteins and human proteins other than factor VIII (see section 5.1).

If symptoms of hypersensitivity occur, patients should be advised to discontinue the use of the medicinal product immediately and contact their physician.

Patients should be informed of the early signs of hypersensitivity reactions including hives, nausea, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis.
In case of shock, standard medical treatment for shock should be implemented.

Inhibitors
The formation of neutralising 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 (BU) per ml of plasma using the modified assay. The risk of developing inhibitors is correlated to the exposure to factor VIII and to genetic factors among others, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days.

Cases of recurrence of inhibitors (low titre) have been observed after switching from one factor VIII product to another in previously treated patients with more than 100 exposure days who have a history of inhibitor development. Therefore, it is recommended to monitor all patients carefully for inhibitor occurrence following any product switch.

In general, all patients treated with coagulation factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests.
If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for the presence of factor VIII inhibitor should be performed. In patients with high levels of inhibitor, 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 haemophilia and factor VIII inhibitors.

Continuous infusion
In a clinical study about the use of continuous infusion in surgeries, heparin was used to prevent thrombophlebitis at the infusion site as with any other long term intravenous infusions.

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

Cardiovascular events
Haemophilic patients with cardiovascular risk factors or diseases may be at the same risk to develop cardiovascular events as non-haemophilic patients when clotting has been normalised by treatment with FVIII. Elevation of FVIII levels following administration, in particular with existing cardiovascular risk factors, might put a patient into the same risk for vessel closure or myocardial infarction as for the non-haemophilic population. Consequently, patients should be evaluated and monitored for cardiac risk factors.

Catheter-related complications
If a central venous access device (CVAD) is required, risk of CVAD-related complications including local infections, bacteremia and catheter site thrombosis should be considered.

Documentation
It is strongly recommended that every time that Helixate NexGen is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the medicinal product.

Paediatric population
The listed warnings and precautions apply both to adults and children.

4.5 Interactions with other medicinal products and other forms of interaction

No interactions of Helixate NexGen with other medicinal products have been reported.

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with Helixate NexGen.

Pregnancy and breast-feeding
Based on the rare occurrence of haemophilia A in women, experience regarding the use of Helixate NexGen during pregnancy and breast-feeding is not available. Therefore, Helixate NexGen should be used during pregnancy and breast-feeding only if clearly indicated.

Fertility
There are no fertility data available.

4.7 Effects on ability to drive or use machines

Helixate NexGen has no influence on the ability to drive or to use machines.

4.8 Undesirable effects

Summary of the safety profile
Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the infusion site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed with recombinant factor VIII products and may in some cases progress to severe anaphylaxis (including shock). In particular the skin related reactions may occur commonly, whereas a progress to severe anaphylaxis (including shock) is considered to be rare.

Patients with haemophilia A may develop neutralising antibodies (inhibitors) to factor VIII. The condition may manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted.

Tabulated list of adverse reactions
The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level).

Frequencies have been evaluated according to the following convention: very common: (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

MedDRA Standard System Organ Class	**Frequency**				
	Very common	**Common**	**Uncommon**	**Rare**	**Very Rare / not known**
Blood and the Lymphatic System Disorders	Inhibitor Formation to FVIII (reported in PUPs and MTPs)*		Inhibitor Formation to FVIII (reported in PTPs in clinical trials and Post Marketing Studies)*		
General Disorders and Administration Site Conditions		Infusion site reaction		Infusion related febrile reaction (pyrexia)	
Immune System Disorders		Skin associated hypersensitivity reactions, (pruritus, urticaria and rash)		Systemic Hypersensitivity reactions (including anaphylactic reaction, nausea, blood pressure abnormal and, dizziness)	
Nervous System Disorders					Dysgeusia

PUPs = previously untreated patients
PTPs = previously treated patients
MTPs = minimally treated patients
* see section below

Description of selected adverse reactions
Inhibitor development
Inhibitor development in previously untreated and treated patients (PUPs / PTPs) has been reported (see section 4.4).

In clinical studies, Helixate NexGen has been used in the treatment of bleeding episodes in 37 previously untreated patients (PUPs) and 23 minimally treated paediatric patients (MTPs, defined as having ≤4 exposure days) with residual FVIII:C < 2 IU/dl. Five out of 37 (14%) PUP and 4 out of 23 (17%) MTP patients treated with Helixate NexGen developed inhibitors within 20 exposure days.

Overall, 9 out of 60 (15%) developed inhibitors. One patient was lost to follow up and one patient developed a low-titre inhibitor during post study follow-up.
In one observational study, the incidence of inhibitor development in previously untreated patients with severe haemophilia A was 64/183 (37.7%) with Helixate NexGen (followed up to 75 exposure days).

In clinical studies with 73 previously treated patients (PTP, defined as having ≥100 exposure days), followed over 4 years, no de-novo inhibitors were observed.
In extensive post-registration observational studies with Helixate NexGen, involving more than 1000 patients the following was observed: Less than 0.2% PTP developed de-novo inhibitors.

Paediatric population
Frequency, type and severity of adverse reactions in children are expected to be the same as in all population groups except for the inhibitor formation.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose with recombinant coagulation factor VIII has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antihemorrhagics: blood coagulation factor VIII, ATC code B02BD02.

Mechanism of action
The factor VIII/von Willebrand factor (vWF) complex consists of two molecules (factor VIII and vWF) with different physiological functions. When infused into a haemophilic patient, factor VIII binds to vWF 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 can be 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.

Pharmacodynamic effects
Determination of activated partial thromboplastin time (aPTT) is a conventional *in vitro* assay method for biological activity of factor VIII. The aPTT is prolonged in all haemophiliacs. The degree and duration of aPTT normalisation observed after administration of Helixate NexGen is similar to that achieved with plasma-derived factor VIII.

Continuous Infusion
It has been shown in a clinical study performed with adult haemophilia A patients who undergo a major surgery that Helixate NexGen can be used for continuous infusion in surgeries (pre-, during and postoperative). In this study heparin was used to prevent thrombophlebitis at the infusion site as with any other long term intravenous infusions.

Hypersensitivity
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 (see sections 4.3 and 4.4).

Immune Tolerance Induction (ITI)
Data on Immune Tolerance Induction have been collected in patients with haemophilia A who had developed inhibitors to FVIII. A retrospective review has been done on 40 patients, and 39 patients were included in a prospective investigator-initiated clinical study. Data show that Helixate NexGen has been used to induce immune tolerance. In patients where immune tolerance was achieved the bleedings could be prevented or controlled with Helixate NexGen again, and the patients could continue with prophylactic treatment as maintenance therapy.

5.2 Pharmacokinetic properties

Absorption
The analysis of all recorded *in vivo* recoveries in previously treated patients demonstrated a mean rise of 2 % per IU/kg body weight for Helixate NexGen. This result is similar to the reported values for factor VIII derived from human plasma.

Distribution and elimination
After administration of Helixate NexGen, peak factor VIII activity decreased by a two-phase exponential decay with a mean terminal half-life of about 15 hours. This is similar to that of plasma-derived factor VIII which has a mean terminal half-life of approx. 13 hours. Additional pharmacokinetic parameters for Helixate NexGen for bolus injection are: mean residence time [MRT (0-48)] of about 22 hours and clearance of about 160 ml/h.Mean baseline clearance for 14 adult patients undergoing major surgeries with continuous infusion are 188 ml/h corresponding to 3.0 ml/h/kg (range 1.6-4.6 ml/h/kg).

5.3 Preclinical safety data

Even doses several fold higher than the recommended clinical dose (related to body weight) failed to demonstrate any acute or subacute toxic effects for Helixate NexGen in laboratory animals (mouse, rat, rabbit, and dog).

Specific studies with repeated administration such as reproduction toxicity, chronic toxicity, and carcinogenicity were not performed with octocog alfa due to the immune response to heterologous proteins in all non-human mammalian species.

No studies were performed on the mutagenic potential of Helixate NexGen, since no mutagenic potential could be detected *in vitro* or *in vivo* for the predecessor product of Helixate NexGen.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder
Glycine
Sodium chloride
Calcium chloride
Histidine
Polysorbate 80
Sucrose

Solvent
Water for injections

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.
Only the provided administration sets can be used because treatment failure can occur as a consequence of human recombinant coagulation factor VIII adsorption to the internal surfaces of some infusion equipment.

6.3 Shelf-life

30 months.

After reconstitution, from a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

However, during *in vitro* studies, the chemical and physical in-use stability has been demonstrated for 24 hours at 30°C in PVC bags for continuous infusion". After reconstitution, the chemical and physical in-use stability has been demonstrated for 3 hours in *in vitro* studies.

Do not refrigerate after reconstitution.

6.4 Special precautions for storage

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

Within its overall shelf life of 30 months the product when kept in its outer carton, may be stored at ambient room temperature (up to 25°C) for a limited period of 12 months. In this case, the product expires at the end of this 12-month period or the expiration date on the product vial, whichever is earlier. The new expiry date must be noted on the top of the outer carton.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container and special equipment for use, administration or implantation

Each package of Helixate NexGen contains:
- one vial with powder (10 ml clear glass type 1 vial with latex-free grey halogenobutyl rubber blend stopper and aluminium seal)
- one vial with solvent (6 ml clear glass type 1 vial with latex-free grey chlorobutyl rubber blend stopper and aluminium seal)
- an additional package with:
  - 1 filter transfer device 20/20 [Mix2Vial]
  - 1 venipuncture set
  - 1 disposable 5 ml syringe
  - 2 alcohol swabs for single use

6.6 Special precautions for disposal and other handling

Detailed instructions for preparation and administration are contained in the package leaflet provided with Helixate NexGen.

Helixate NexGen powder should only be reconstituted with the supplied solvent (5.0 ml water for injections) using the supplied sterile Mix2Vial filter transfer device. For infusion, the product must be prepared under aseptic conditions. If any component of the package is opened or damaged, do not use this component.
Gently rotate the vial until all powder is dissolved. After reconstitution the solution is clear.
Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Do not use Helixate NexGen if you notice visible particulate matter or turbidity.

After reconstitution, the solution is drawn through the Mix2Vial filter transfer device into the sterile disposable syringe (both supplied). Helixate NexGen should be reconstituted and administered with the components provided with each package.

The reconstituted product must be filtered prior to administration to remove potential particulate matter in the solution. Filtering is achieved by using the Mix2Vial adapter.

For single use only. Any unused solution must be discarded.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bayer Pharma AG
13342 Berlin
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/144/005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 August 2000
Date of latest renewal: 06 August 2010

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERRESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance

Bayer Corporation (license holder)
Bayer HealthCare LLC
800 Dwight Way
Berkeley, CA 94710
USA

Name and address of the manufacturer(s) responsible for batch release

Bayer HealthCare Manufacturing S.r.l.
Via delle Groane 126
20024 Garbagnate Milanese (MI)
Italy

B CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Helixate NexGen 250 IU powder and solvent for solution for injection

Recombinant coagulation factor VIII (octocog alfa)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 250 IU octocog alfa (100 IU/ml after reconstitution).

3. LIST OF EXCIPIENTS

Glycine, sodium chloride, calcium chloride, histidine, polysorbate 80, sucrose.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial with powder for solution for injection.
1 vial with 2.5 ml water for injections.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use, single dose administration only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE,

EXP
EXP (End of the 12 month period, if stored at room temperature): .....
Do not use after this date.

May be stored at temperatures up to 25°C for up to 12 months within the expiry date indicated on the label. Note the new expiry date on the top of the carton. After reconstitution, the product must be used within 3 hours. Do not refrigerate after reconstitution.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C). Do not freeze.

Keep the vials in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer Pharma AG
13342 Berlin
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/144/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Helixate NexGen 250

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL WITH POWDER FOR SOLUTION FOR INJECTION

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Helixate NexGen 250 IU powder for solution for injection

Recombinant coagulation factor VIII (octocog alfa)

Intravenous use.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

250 IU octocog alfa (100 IU/ml after reconstitution).

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL WITH 2.5 ML WATER FOR INJECTIONS

1. NAME OF THE MEDICINAL PRODUCT AND IF NECESSARY ROUTE(S) OF ADMINISTRATION

Water for injections

2. METHOD OF ADMINISTRATION

For reconstitution of Helixate NexGen, see package leaflet. Use entire content.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2.5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Helixate NexGen 500 IU powder and solvent for solution for injection

Recombinant coagulation factor VIII (octocog alfa)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 500 IU octocog alfa (200 IU/ml after reconstitution).

3. LIST OF EXCIPIENTS

Glycine, sodium chloride, calcium chloride, histidine, polysorbate 80, sucrose.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial with powder for solution for injection.
1 vial with 2.5 ml water for injections.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use, single dose administration only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE,

EXP
EXP (End of the 12 month period, if stored at room temperature): .....
Do not use after this date.

May be stored at temperatures up to 25°C for up to 12 months within the expiry date indicated on the label. Note the new expiry date on the top of the carton. After reconstitution, the product must be used within 3 hours. Do not refrigerate after reconstitution.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C). Do not freeze.

Keep the vials in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer Pharma AG
13342 Berlin
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/144/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Helixate NexGen 500

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL WITH POWDER FOR SOLUTION FOR INJECTION

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Helixate NexGen 500 IU powder for solution for injection

Recombinant coagulation factor VIII (octocog alfa)

Intravenous use.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

500 IU octocog alfa (200 IU/ml after reconstitution).

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL WITH 2.5 ML WATER FOR INJECTIONS

1. NAME OF THE MEDICINAL PRODUCT AND IF NECESSARY ROUTE(S) OF ADMINISTRATION

Water for injections

2. METHOD OF ADMINISTRATION

For reconstitution of Helixate NexGen, see package leaflet. Use entire content.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2.5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Helixate NexGen 1000 IU powder and solvent for solution for injection

Recombinant coagulation factor VIII (octocog alfa)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 1000 IU octocog alfa (400 IU/ml after reconstitution).

3. LIST OF EXCIPIENTS

Glycine, sodium chloride, calcium chloride, histidine, polysorbate 80, sucrose.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial with powder for solution for injection.
1 vial with 2.5 ml water for injections.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use, single dose administration only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE,

EXP
EXP (End of the 12 month period, if stored at room temperature): .....
Do not use after this date.

May be stored at temperatures up to 25°C for up to 12 months within the expiry date indicated on the label. Note the new expiry date on the top of the carton. After reconstitution, the product must be used within 3 hours. Do not refrigerate after reconstitution.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C). Do not freeze.

Keep the vials in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer Pharma AG
13342 Berlin
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/144/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Helixate NexGen 1000

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL WITH POWDER FOR SOLUTION FOR INJECTION

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Helixate NexGen 1000 IU powder for solution for injection

Recombinant coagulation factor VIII (octocog alfa)

Intravenous use.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1000 IU octocog alfa (400 IU/ml after reconstitution).

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL WITH 2.5 ML WATER FOR INJECTIONS

1. NAME OF THE MEDICINAL PRODUCT AND IF NECESSARY ROUTE(S) OF ADMINISTRATION

Water for injections

2. METHOD OF ADMINISTRATION

For reconstitution of Helixate NexGen, see package leaflet. Use entire content.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2.5 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Helixate NexGen 2000 IU powder and solvent for solution for injection

Recombinant coagulation factor VIII (octocog alfa)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 2000 IU octocog alfa (400 IU/ml after reconstitution).

3. LIST OF EXCIPIENTS

Glycine, sodium chloride, calcium chloride, histidine, polysorbate 80, sucrose.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial with powder for solution for injection.
1 vial with 5.0 ml water for injections.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use, single dose administration only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE,

EXP
EXP (End of the 12 month period, if stored at room temperature): .....
Do not use after this date.

May be stored at temperatures up to 25°C for up to 12 months within the expiry date indicated on the label. Note the new expiry date on the top of the carton. After reconstitution, the product must be used within 3 hours. Do not refrigerate after reconstitution.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C). Do not freeze.

Keep the vials in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer Pharma AG
13342 Berlin
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/144/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Helixate NexGen 2000

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL WITH POWDER FOR SOLUTION FOR INJECTION

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Helixate NexGen 2000 IU powder for solution for injection

Recombinant coagulation factor VIII (octocog alfa)

Intravenous use.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

2000 IU octocog alfa (400 IU/ml after reconstitution).

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL WITH 5.0 ML WATER FOR INJECTIONS

1. NAME OF THE MEDICINAL PRODUCT AND IF NECESSARY ROUTE(S) OF ADMINISTRATION

Water for injections

2. METHOD OF ADMINISTRATION

For reconstitution of Helixate NexGen, see package leaflet. Use entire content.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5.0 ml

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Helixate NexGen 3000 IU powder and solvent for solution for injection

Recombinant coagulation factor VIII (octocog alfa)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 vial: 3000 IU octocog alfa (600 IU/ml after reconstitution).

3. LIST OF EXCIPIENTS

Glycine, sodium chloride, calcium chloride, histidine, polysorbate 80, sucrose.

4. PHARMACEUTICAL FORM AND CONTENTS

1 vial with powder for solution for injection.
1 vial with 5.0 ml water for injections.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For intravenous use, single dose administration only.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE,

EXP
EXP (End of the 12 month period, if stored at room temperature): .....
Do not use after this date.

May be stored at temperatures up to 25°C for up to 12 months within the expiry date indicated on the label. Note the new expiry date on the top of the carton. After reconstitution, the product must be used within 3 hours. Do not refrigerate after reconstitution.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C - 8°C). Do not freeze.

Keep the vials in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused solution must be discarded.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Bayer Pharma AG
13342 Berlin
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/144/005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Helixate NexGen 3000

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL WITH POWDER FOR SOLUTION FOR INJECTION

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Helixate NexGen 3000 IU powder for solution for injection

Recombinant coagulation factor VIII (octocog alfa)

Intravenous use.

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3000 IU octocog alfa (600 IU/ml after reconstitution).

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL WITH 5.0 ML WATER FOR INJECTIONS

1. NAME OF THE MEDICINAL PRODUCT AND IF NECESSARY ROUTE(S) OF ADMINISTRATION

Water for injections

2. METHOD OF ADMINISTRATION

For reconstitution of Helixate NexGen, see package leaflet. Use entire content.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

5.0 ml

6. OTHER

B. PACKAGE LEAFLET

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 because it contains important information for you.
- 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 only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Helixate NexGen 250 IU is and what it is used for

Helixate NexGen 250 IU contains the active substance human recombinant coagulation factor VIII (octocog alfa).

Helixate NexGen is used for treatment and prophylaxis of bleeding adults, adolescents and children of all ages with haemophilia A (congenital factor VIII deficiency).
This preparation does not contain von Willebrand factor and is therefore not to be used in von Willebrand's disease.

The vial contains a dry white to slightly yellow powder or cake, as well as water for injections to be used to reconstitute the contents of the vial.

The vial with powder contains 250 IU (International Units) of octocog alfa. After reconstitution with the water for injection, each vial contains octocog alfa 100 IU/ml.

2. What you need to know before you use Helixate NexGen 250 IU

Do not use Helixate NexGen 250 IU
- If you are allergic to octocog alfa or to any of the other ingredients of this medicine *(listed in section 6 and end of section 2*).
- If you are allergic to mouse or hamster protein.

If you are unsure about this, ask your doctor.

Warnings and precautions
Talk to your doctor or pharmacist before using Helixate NexGen 250 IU.

Take special care with Helixate NexGen 250 IU

- If you experience tightness in the chest, feeling dizzy, feeling sick or faint, or experience dizziness on standing, you may be experiencing a rare severe sudden allergic reaction (a so-called anaphylactic reaction) to this medicine. If this occurs, **stop administering the product** immediately and seek medical advice.

- Your doctor may carry out tests to ensure that your current dose of this medicine provides adequate factor VIII levels.

- If your bleeding is not being controlled with your usual dose of this medicine, consult your doctor immediately. You may have developed factor VIII inhibitors and your doctor may carry out tests to confirm this. Factor VIII inhibitors are antibodies in the blood which block the factor VIII you are using, and makes it less effective to prevent and control 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.

- If you have been told you have heart disease or are at risk for heart disease, tell your doctor or pharmacist.

- If for the administration of Helixate NexGen you will require a central venous access device (CVAD), the risk of CVAD-related complications including local infections, bacteria in the blood (bacteremia) and the formation of a blood clot in the blood vessel (thrombosis) where the catheter is inserted should be considered by your doctor.

Other medicines and Helixate NexGen 250 IU
Interactions with other medicines are not known. However, please tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Pregnancy, breast-feeding and fertility
Experience regarding fertility or the use of Helixate NexGen during pregnancy and breast-feeding is not available. Therefore, if you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.

Driving and using machines
No effects on ability to drive or use machines have been observed.

Helixate NexGen 250 IU contains sodium
This medicinal product contains less than 23 mg sodium per vial, i.e. essentially “sodium-free”.

3. How to use Helixate NexGen 250 IU

- Always use this medicine exactly as described in this leaflet or as your doctor or pharmacist have told you. Check with your doctor or pharmacist if you are not sure.

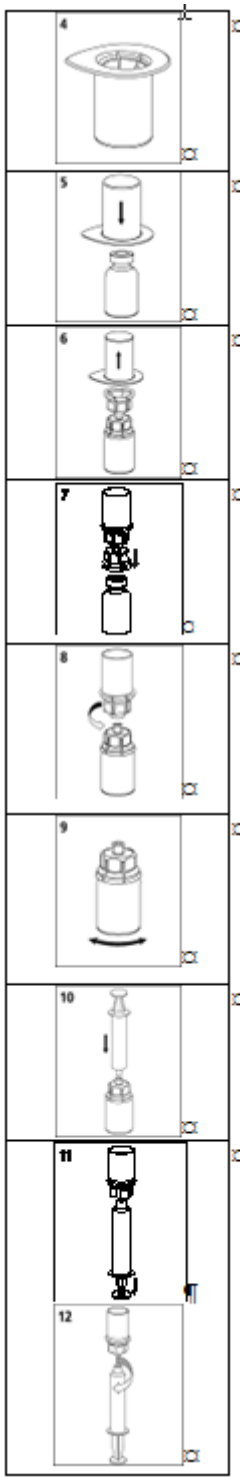
- This medicine is intended for intravenous administration only and should be administered within 3 hours after reconstitution.

- You must use aseptic conditions (meaning clean and germ free) during reconstitution and administration. Use only the medical devices for reconstitution and administration that are provided with each package of this medicine. If these components cannot be used, please contact your doctor. If any component of the package is opened or damaged, do not use it.

- You must filter the reconstituted product before administration to remove potential particulate matter in the solution. Filtering is achieved by using the Mix2Vial adapter.

- This medicine 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:

Reconstitution and administration



1. Wash your 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 solvent 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. Do **not** remove the Mix2Vial from the blister package!
5. Place the solvent vial on an even, clean surface and hold the vial tight. Take the Mix2Vial together with the blister package and push the spike of the blue adapter end **straight down** through the solvent vial stopper.
6. Carefully remove the blister package from the Mix2Vial set by holding at the rim, and pulling **vertically** upwards. Make sure that you only pull away the blister package and not the Mix2Vial set.
7. Place the product vial on an even and firm surface. Invert the solvent vial with the Mix2Vial set attached and push the spike of the transparent adapter end **straight down** through the product vial stopper. The solvent will automatically flow into the product vial.
8. With one hand grasp the product-side of the Mix2Vial set and with the other hand grasp the solvent-side and unscrew the set carefully into two pieces. Discard the solvent vial with the blue Mix2Vial adapter attached.
9. Gently swirl the product vial with the transparent adapter attached until the substance is fully dissolved. Do not shake. Inspect visually for particulate matter and discoloration prior to administration. Do not use solutions containing visible particles or that are cloudy.
10. Draw air into an empty, sterile syringe. While the product vial is upright, connect the syringe to the Mix2Vial´s Luer Lock fitting. Inject air into the product vial.
11. While keeping the syringe plunger pressed, turn the system upside down and draw the solution into the syringe by pulling the plunger back slowly.
12. Now that the solution has been transferred into the syringe, firmly hold on to the barrel of the syringe (keeping the syringe plunger facing down) and disconnect the transparent Mix2Vial adapter from the syringe. Hold the syringe upright and push the plunger until no air is left in the syringe.
13. Apply a tourniquet.
14. Determine the point of injection and prepare antiseptically.
15. Puncture the vein and secure the venipuncture set with a plaster.
16 Let blood flow back to the open end of the venipuncture set and then attach the syringe with the solution. Make sure that no blood enters the syringe.
17. Remove tourniquet.
18. Inject the solution intravenously over several minutes, keeping an eye on the position of the needle. The speed of administration should be based on the patient’s comfort, but should not be faster than 2ml/min maximum rate of infusion.
19. If a further dose needs to be administered, use a new syringe with product reconstituted as described above.

20. 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.

Treatment of bleeding
How much Helixate NexGen 250 IU you should use and how often you should use it depends on many factors such as your weight, the severity of your haemophilia, where the bleed is and how serious it is, whether you have inhibitors and how high the inhibitor titre is and the factor VIII level that is needed.

Your doctor will calculate the dose of this medicine and how frequently you should use it to get the necessary level of factor VIII activity in your blood. He/she should always adjust the amount of this medicine to be administered and the frequency of administration according to your individual needs. Under certain circumstances larger amounts than those calculated may be required, especially for the initial dose.

Prevention of bleeding
If you are using Helixate NexGen to prevent bleeding (prophylaxis), your doctor will calculate the dose for you. This will usually be in the range of 20 to 40 IU of octocog alfa per kg of body weight, given every 2 to 3 days. However, in some cases, especially for younger patients, shorter dose intervals or higher doses may be necessary.

Laboratory tests
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. For major surgery in particular, close monitoring of the substitution therapy by means of coagulation analysis must be carried out.

If bleeding is not controlled
If the factor VIII level in your plasma fails to reach expected levels, or if bleeding is not controlled after apparently adequate dose, you may have developed factor VIII inhibitors. This must be checked by an experienced doctor.
If you have the impression that the effect of this medicine is too strong or too weak, talk to your doctor.

Patients with inhibitors
If you have been told by your doctor that you have developed factor VIII inhibitors you may need to use a larger amount of this medicine to control bleeding. If this dose does not control your bleeding your doctor may consider giving you an additional product, factor VIIa concentrate or (activated) prothrombin complex concentrate.
These treatments should be prescribed by doctors with experience in the care of patients with haemophilia A. Speak to your doctor if you would like further information on this.
Do not increase your dose of medicine you use to control your bleeding without consulting your doctor.

Speed of administration
This medicine 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).

Duration of treatment
Your doctor will tell you, how often and at what intervals this medicine is to be administered.

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

If you use more Helixate NexGen 250 IU than you should
No cases 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 your next dose immediately and continue at regular intervals as advised by your doctor.
- **Do not** take a double dose to make up for a forgotten dose**.**

If you want to stop using Helixate NexGen 250 IU
Do not stop using Helixate NexGen without consulting your doctor.

Documentation
It is recommended that every time that you use Helixate NexGen, the name and batch number of the product are documented.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most **serious** side effects are **hypersensitivity reactions** or anaphylactic shock (rare side effect). If allergic or anaphylactic reactions occur, the injection/infusion should be **stopped immediately**. **Please consult your doctor immediately**.

Overall list of possible side effects:

Very common:
may affect more than 1 in 10 users
- formation of neutralising antibodies to factor VIII (inhibitors) in previously untreated patients

Common:
may affect up to 1 in 10 users**:**
- rash/itchy rash
- local reactions where you injected the medication (e.g. burning sensation, temporary redness)

Uncommon
may affect up to 1 in 100 users
- formation of neutralising antibodies to factor VIII (inhibitors) in previously treated patients

Rare:
may affect up to 1 in 1,000 users
- hypersensitivity reactions including severe sudden allergic reaction (which may include hives, nausea, urticaria, angioedema, chills, flushing, headache, lethargy, wheezing or difficulty breathing, restlessness, tachycardia, tingling or anaphylactic shock, 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)
- fever

Not known:
frequency cannot be estimated from the available data
- dysgeusia

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.**

Antibodies (Inhibitors)
The formation of neutralising antibodies to factor VIII (inhibitors) is a known complication in the treatment of patients with haemophilia A. Your doctor may wish to carry out tests to monitor inhibitor development.

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

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Helixate NexGen 250 IU

Keep this medicine out of the sight and reach 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.

Within the expiry date indicated on the label, this medicine when kept in its outer carton may be stored at ambient room temperature (up to 25°C) for a limited period of 12 months. In this case, this medicine expires at the end of this 12-month period or the expiration date on the product vial, whichever is earlier. The new expiry date must be noted on the outer carton.

Do not refrigerate the solution after reconstitution. The reconstituted solution must be used within 3 hours. This product is for single use only. Any unused solution must be discarded.

Do not use this medicine 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 this medicine if you notice any particles or the solution is cloudy.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Helixate NexGen 250 IU contains

Powder
The **active** substance is human coagulation factor VIII (octocog alfa) produced by recombinant DNA technology.
The **other** ingredients are glycine, sodium chloride, calcium chloride, histidine, polysorbate 80, and sucrose (*see end of section 2)*.

Solvent
Water for injections, sterilised.

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

Helixate NexGen 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
Bayer Pharma AG
13342 Berlin
Germany

Manufacturer
Bayer HealthCare Manufacturing S.r.l.
Via delle Groane 126
20024 Garbagnate Milanese (MI)
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This leaflet was last revised in {**MM/YYYY**}

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

Package Leaflet: Information for the user

Helixate NexGen 500 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 because it contains important information for you.
- 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 only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Helixate NexGen 500 IU is and what it is used for

Helixate NexGen 500 IU contains the active substance human recombinant coagulation factor VIII (octocog alfa).

Helixate NexGen is used for treatment and prophylaxis of bleeding adults, adolescents and children of all ages with haemophilia A (congenital factor VIII deficiency).
This preparation does not contain von Willebrand factor and is therefore not to be used in von Willebrand's disease.

The vial contains a dry white to slightly yellow powder or cake, as well as water for injections to be used to reconstitute the contents of the vial.

The vial with powder contains 500 IU (International Units) of octocog alfa. After reconstitution with the water for injection, each vial contains octocog alfa 200 IU/ml.

2. What you need to know before you use Helixate NexGen 500 IU

Do not use Helixate NexGen 500 IU
- If you are allergic to octocog alfa or to any of the other ingredients of this medicine *(listed in section 6 and end of section 2*).
- If you are allergic to mouse or hamster protein.

If you are unsure about this, ask your doctor.

Warnings and precautions
Talk to your doctor or pharmacist before using Helixate NexGen 500 IU.

Take special care with Helixate NexGen 500 IU

- If you experience tightness in the chest, feeling dizzy, feeling sick or faint, or experience dizziness on standing, you may be experiencing a rare severe sudden allergic reaction (a so-called anaphylactic reaction) to this medicine. If this occurs, **stop administering the product** immediately and seek medical advice.

- Your doctor may carry out tests to ensure that your current dose of this medicine provides adequate factor VIII levels.

- If your bleeding is not being controlled with your usual dose of this medicine, consult your doctor immediately. You may have developed factor VIII inhibitors and your doctor may carry out tests to confirm this. Factor VIII inhibitors are antibodies in the blood which block the factor VIII you are using, and makes it less effective to prevent and control 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.

- If you have been told you have heart disease or are at risk for heart disease, tell your doctor or pharmacist.

- If for the administration of Helixate NexGen you will require a central venous access device (CVAD), the risk of CVAD-related complications including local infections, bacteria in the blood (bacteremia) and the formation of a blood clot in the blood vessel (thrombosis) where the catheter is inserted should be considered by your doctor.

Other medicines and Helixate NexGen 500 IU
Interactions with other medicines are not known. However, please tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Pregnancy, breast-feeding and fertility
Experience regarding fertility or the use of Helixate NexGen during pregnancy and breast-feeding is not available. Therefore, if you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.

Driving and using machines
No effects on ability to drive or use machines have been observed.

Helixate NexGen 500 IU contains sodium
This medicinal product contains less than 23 mg sodium per vial, i.e. essentially “sodium-free”.

3. How to use Helixate NexGen 500 IU

- Always use this medicine exactly as described in this leaflet or as your doctor or pharmacist have told you. Check with your doctor or pharmacist if you are not sure.

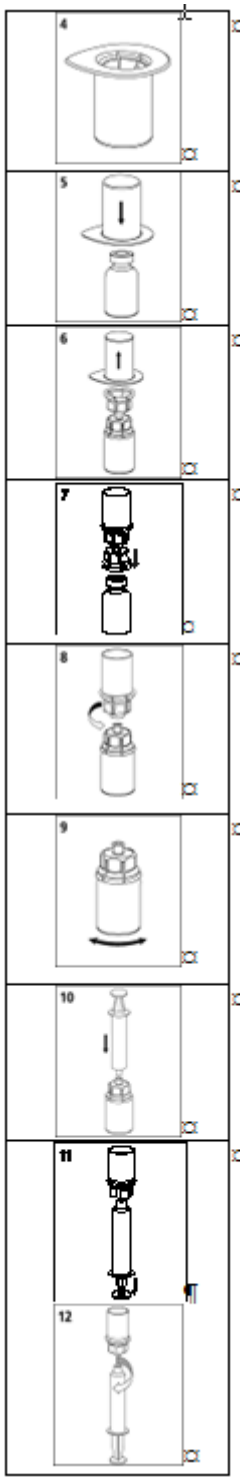
- This medicine is intended for intravenous administration only and should be administered within 3 hours after reconstitution.

- You must use aseptic conditions (meaning clean and germ free) during reconstitution and administration. Use only the medical devices for reconstitution and administration that are provided with each package of this medicine. If these components cannot be used, please contact your doctor. If any component of the package is opened or damaged, do not use it.

- You must filter the reconstituted product before administration to remove potential particulate matter in the solution. Filtering is achieved by using the Mix2Vial adapter.

- This medicine 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:

Reconstitution and administration



1. Wash your 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 solvent 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. Do **not** remove the Mix2Vial from the blister package!
5. Place the solvent vial on an even, clean surface and hold the vial tight. Take the Mix2Vial together with the blister package and push the spike of the blue adapter end **straight down** through the solvent vial stopper.
6. Carefully remove the blister package from the Mix2Vial set by holding at the rim, and pulling **vertically** upwards. Make sure that you only pull away the blister package and not the Mix2Vial set.
7. Place the product vial on an even and firm surface. Invert the solvent vial with the Mix2Vial set attached and push the spike of the transparent adapter end **straight down** through the product vial stopper. The solvent will automatically flow into the product vial.
8. With one hand grasp the product-side of the Mix2Vial set and with the other hand grasp the solvent-side and unscrew the set carefully into two pieces. Discard the solvent vial with the blue Mix2Vial adapter attached.
9. Gently swirl the product vial with the transparent adapter attached until the substance is fully dissolved. Do not shake. Inspect visually for particulate matter and discoloration prior to administration. Do not use solutions containing visible particles or that are cloudy.
10. Draw air into an empty, sterile syringe. While the product vial is upright, connect the syringe to the Mix2Vial´s Luer Lock fitting. Inject air into the product vial.
11. While keeping the syringe plunger pressed, turn the system upside down and draw the solution into the syringe by pulling the plunger back slowly.
12. Now that the solution has been transferred into the syringe, firmly hold on to the barrel of the syringe (keeping the syringe plunger facing down) and disconnect the transparent Mix2Vial adapter from the syringe. Hold the syringe upright and push the plunger until no air is left in the syringe.
13. Apply a tourniquet.
14. Determine the point of injection and prepare antiseptically.
15. Puncture the vein and secure the venipuncture set with a plaster.
16 Let blood flow back to the open end of the venipuncture set and then attach the syringe with the solution. Make sure that no blood enters the syringe.
17. Remove tourniquet.
18. Inject the solution intravenously over several minutes, keeping an eye on the position of the needle. The speed of administration should be based on the patient’s comfort, but should not be faster than 2ml/min maximum rate of infusion.
19. If a further dose needs to be administered, use a new syringe with product reconstituted as described above.

20. 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.

Treatment of bleeding
How much Helixate NexGen 500 IU you should use and how often you should use it depends on many factors such as your weight, the severity of your haemophilia, where the bleed is and how serious it is, whether you have inhibitors and how high the inhibitor titre is and the factor VIII level that is needed.

Your doctor will calculate the dose of this medicine and how frequently you should use it to get the necessary level of factor VIII activity in your blood. He/she should always adjust the amount of this medicine to be administered and the frequency of administration according to your individual needs. Under certain circumstances larger amounts than those calculated may be required, especially for the initial dose.

Prevention of bleeding
If you are using Helixate NexGen to prevent bleeding (prophylaxis), your doctor will calculate the dose for you. This will usually be in the range of 20 to 40 IU of octocog alfa per kg of body weight, given every 2 to 3 days. However, in some cases, especially for younger patients, shorter dose intervals or higher doses may be necessary.

Laboratory tests
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. For major surgery in particular, close monitoring of the substitution therapy by means of coagulation analysis must be carried out.

If bleeding is not controlled
If the factor VIII level in your plasma fails to reach expected levels, or if bleeding is not controlled after apparently adequate dose, you may have developed factor VIII inhibitors. This must be checked by an experienced doctor.
If you have the impression that the effect of this medicine is too strong or too weak, talk to your doctor.

Patients with inhibitors
If you have been told by your doctor that you have developed factor VIII inhibitors you may need to use a larger amount of this medicine to control bleeding. If this dose does not control your bleeding your doctor may consider giving you an additional product, factor VIIa concentrate or (activated) prothrombin complex concentrate.
These treatments should be prescribed by doctors with experience in the care of patients with haemophilia A. Speak to your doctor if you would like further information on this.
Do not increase your dose of medicine you use to control your bleeding without consulting your doctor.

Speed of administration
This medicine 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).

Duration of treatment
Your doctor will tell you, how often and at what intervals this medicine is to be administered.

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

If you use more Helixate NexGen 500 IU than you should
No cases of overdose with recombinant coagulation factor VIII have been reported.

If you have used more Helixate NexGen 500 IU than you should, please inform your doctor.

If you forget to use Helixate NexGen 500 IU
- Proceed with your next dose immediately and continue at regular intervals as advised by your doctor.
- **Do not** take a double dose to make up for a forgotten dose**.**

If you want to stop using Helixate NexGen 500 IU
Do not stop using Helixate NexGen without consulting your doctor.

Documentation
It is recommended that every time that you use Helixate NexGen, the name and batch number of the product are documented.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most **serious** side effects are **hypersensitivity reactions** or anaphylactic shock (rare side effect). If allergic or anaphylactic reactions occur, the injection/infusion should be **stopped immediately**. **Please consult your doctor immediately**.

Overall list of possible side effects:

Very common:
may affect more than 1 in 10 users
- formation of neutralising antibodies to factor VIII (inhibitors) in previously untreated patients

Common:
may affect up to 1 in 10 users**:**
- rash/itchy rash
- local reactions where you injected the medication (e.g. burning sensation, temporary redness)

Uncommon
may affect up to 1 in 100 users
- formation of neutralising antibodies to factor VIII (inhibitors) in previously treated patients

Rare:
may affect up to 1 in 1,000 users
- hypersensitivity reactions including severe sudden allergic reaction (which may include hives, nausea, urticaria, angioedema, chills, flushing, headache, lethargy, wheezing or difficulty breathing, restlessness, tachycardia, tingling or anaphylactic shock, 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)
- fever

Not known:
frequency cannot be estimated from the available data
- dysgeusia

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.**

Antibodies (Inhibitors)
The formation of neutralising antibodies to factor VIII (inhibitors) is a known complication in the treatment of patients with haemophilia A. Your doctor may wish to carry out tests to monitor inhibitor development.

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

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Helixate NexGen 500 IU

Keep this medicine out of the sight and reach 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.

Within the expiry date indicated on the label, this medicine when kept in its outer carton may be stored at ambient room temperature (up to 25°C) for a limited period of 12 months. In this case, this medicine expires at the end of this 12-month period or the expiration date on the product vial, whichever is earlier. The new expiry date must be noted on the outer carton.

Do not refrigerate the solution after reconstitution. The reconstituted solution must be used within 3 hours. This product is for single use only. Any unused solution must be discarded.

Do not use this medicine 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 this medicine if you notice any particles or the solution is cloudy.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Helixate NexGen 500 IU contains

Powder
The **active** substance is human coagulation factor VIII (octocog alfa) produced by recombinant DNA technology.
The **other** ingredients are glycine, sodium chloride, calcium chloride, histidine, polysorbate 80, and sucrose (*see end of section 2)*.

Solvent
Water for injections, sterilised.

What Helixate NexGen 500 IU looks like and content of the pack

Helixate NexGen 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 500 IU.

Marketing Authorisation Holder
Bayer Pharma AG
13342 Berlin
Germany

Manufacturer
Bayer HealthCare Manufacturing S.r.l.
Via delle Groane 126
20024 Garbagnate Milanese (MI)
Italy

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

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This leaflet was last revised in {**MM/YYYY**}

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

Package Leaflet: Information for the user

Helixate NexGen 1000 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 because it contains important information for you.
- 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 only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Helixate NexGen 1000 IU is and what it is used for

Helixate NexGen 1000 IU contains the active substance human recombinant coagulation factor VIII (octocog alfa).

Helixate NexGen is used for treatment and prophylaxis of bleeding adults, adolescents and children of all ages with haemophilia A (congenital factor VIII deficiency).
This preparation does not contain von Willebrand factor and is therefore not to be used in von Willebrand's disease.

The vial contains a dry white to slightly yellow powder or cake, as well as water for injections to be used to reconstitute the contents of the vial.

The vial with powder contains 1000 IU (International Units) of octocog alfa. After reconstitution with the water for injection, each vial contains octocog alfa 400 IU/ml.

2. What you need to know before you use Helixate NexGen 1000 IU

Do not use Helixate NexGen 1000 IU
- If you are allergic to octocog alfa or to any of the other ingredients of this medicine *(listed in section 6 and end of section 2*).
- If you are allergic to mouse or hamster protein.

If you are unsure about this, ask your doctor.

Warnings and precautions
Talk to your doctor or pharmacist before using Helixate NexGen 1000 IU.

Take special care with Helixate NexGen 1000 IU

- If you experience tightness in the chest, feeling dizzy, feeling sick or faint, or experience dizziness on standing, you may be experiencing a rare severe sudden allergic reaction (a so-called anaphylactic reaction) to this medicine. If this occurs, **stop administering the product** immediately and seek medical advice.

- Your doctor may carry out tests to ensure that your current dose of this medicine provides adequate factor VIII levels.

- If your bleeding is not being controlled with your usual dose of this medicine, consult your doctor immediately. You may have developed factor VIII inhibitors and your doctor may carry out tests to confirm this. Factor VIII inhibitors are antibodies in the blood which block the factor VIII you are using, and makes it less effective to prevent and control 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.

- If you have been told you have heart disease or are at risk for heart disease, tell your doctor or pharmacist.

- If for the administration of Helixate NexGen you will require a central venous access device (CVAD), the risk of CVAD-related complications including local infections, bacteria in the blood (bacteremia) and the formation of a blood clot in the blood vessel (thrombosis) where the catheter is inserted should be considered by your doctor.

Other medicines and Helixate NexGen 1000 IU
Interactions with other medicines are not known. However, please tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Pregnancy, breast-feeding and fertility
Experience regarding fertility or the use of Helixate NexGen during pregnancy and breast-feeding is not available. Therefore, if you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.

Driving and using machines
No effects on ability to drive or use machines have been observed.

Helixate NexGen 1000 IU contains sodium
This medicinal product contains less than 23 mg sodium per vial, i.e. essentially “sodium-free”.

3. How to use Helixate NexGen 1000 IU

- Always use this medicine exactly as described in this leaflet or as your doctor or pharmacist have told you. Check with your doctor or pharmacist if you are not sure.

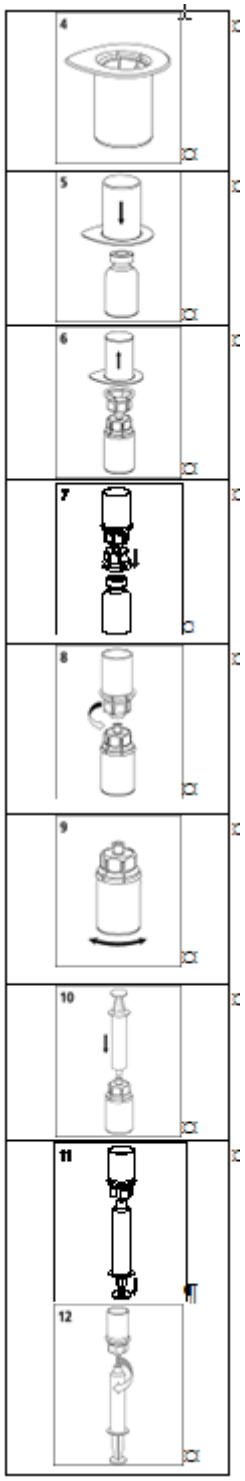
- This medicine is intended for intravenous administration only and should be administered within 3 hours after reconstitution.

- You must use aseptic conditions (meaning clean and germ free) during reconstitution and administration. Use only the medical devices for reconstitution and administration that are provided with each package of this medicine. If these components cannot be used, please contact your doctor. If any component of the package is opened or damaged, do not use it.

- You must filter the reconstituted product before administration to remove potential particulate matter in the solution. Filtering is achieved by using the Mix2Vial adapter.

- This medicine 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:

Reconstitution and administration



1. Wash your 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 solvent 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. Do **not** remove the Mix2Vial from the blister package!
5. Place the solvent vial on an even, clean surface and hold the vial tight. Take the Mix2Vial together with the blister package and push the spike of the blue adapter end **straight down** through the solvent vial stopper.
6. Carefully remove the blister package from the Mix2Vial set by holding at the rim, and pulling **vertically** upwards. Make sure that you only pull away the blister package and not the Mix2Vial set.
7. Place the product vial on an even and firm surface. Invert the solvent vial with the Mix2Vial set attached and push the spike of the transparent adapter end **straight down** through the product vial stopper. The solvent will automatically flow into the product vial.
8. With one hand grasp the product-side of the Mix2Vial set and with the other hand grasp the solvent-side and unscrew the set carefully into two pieces. Discard the solvent vial with the blue Mix2Vial adapter attached.
9. Gently swirl the product vial with the transparent adapter attached until the substance is fully dissolved. Do not shake. Inspect visually for particulate matter and discoloration prior to administration. Do not use solutions containing visible particles or that are cloudy.
10. Draw air into an empty, sterile syringe. While the product vial is upright, connect the syringe to the Mix2Vial´s Luer Lock fitting. Inject air into the product vial.
11. While keeping the syringe plunger pressed, turn the system upside down and draw the solution into the syringe by pulling the plunger back slowly.
12. Now that the solution has been transferred into the syringe, firmly hold on to the barrel of the syringe (keeping the syringe plunger facing down) and disconnect the transparent Mix2Vial adapter from the syringe. Hold the syringe upright and push the plunger until no air is left in the syringe.
13. Apply a tourniquet.
14. Determine the point of injection and prepare antiseptically.
15. Puncture the vein and secure the venipuncture set with a plaster.
16 Let blood flow back to the open end of the venipuncture set and then attach the syringe with the solution. Make sure that no blood enters the syringe.
17. Remove tourniquet.
18. Inject the solution intravenously over several minutes, keeping an eye on the position of the needle. The speed of administration should be based on the patient’s comfort, but should not be faster than 2ml/min maximum rate of infusion.
19. If a further dose needs to be administered, use a new syringe with product reconstituted as described above.

20. 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.

Treatment of bleeding
How much Helixate NexGen 1000 IU you should use and how often you should use it depends on many factors such as your weight, the severity of your haemophilia, where the bleed is and how serious it is, whether you have inhibitors and how high the inhibitor titre is and the factor VIII level that is needed.

Your doctor will calculate the dose of this medicine and how frequently you should use it to get the necessary level of factor VIII activity in your blood. He/she should always adjust the amount of this medicine to be administered and the frequency of administration according to your individual needs. Under certain circumstances larger amounts than those calculated may be required, especially for the initial dose.

Prevention of bleeding
If you are using Helixate NexGen to prevent bleeding (prophylaxis), your doctor will calculate the dose for you. This will usually be in the range of 20 to 40 IU of octocog alfa per kg of body weight, given every 2 to 3 days. However, in some cases, especially for younger patients, shorter dose intervals or higher doses may be necessary.

Laboratory tests
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. For major surgery in particular, close monitoring of the substitution therapy by means of coagulation analysis must be carried out.

If bleeding is not controlled
If the factor VIII level in your plasma fails to reach expected levels, or if bleeding is not controlled after apparently adequate dose, you may have developed factor VIII inhibitors. This must be checked by an experienced doctor.
If you have the impression that the effect of this medicine is too strong or too weak, talk to your doctor.

Patients with inhibitors
If you have been told by your doctor that you have developed factor VIII inhibitors you may need to use a larger amount of this medicine to control bleeding. If this dose does not control your bleeding your doctor may consider giving you an additional product, factor VIIa concentrate or (activated) prothrombin complex concentrate.
These treatments should be prescribed by doctors with experience in the care of patients with haemophilia A. Speak to your doctor if you would like further information on this.
Do not increase your dose of medicine you use to control your bleeding without consulting your doctor.

Speed of administration
This medicine 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).

Duration of treatment
Your doctor will tell you, how often and at what intervals this medicine is to be administered.

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

If you use more Helixate NexGen 1000 IU than you should
No cases of overdose with recombinant coagulation factor VIII have been reported.

If you have used more Helixate NexGen 1000 IU than you should, please inform your doctor.

If you forget to use Helixate NexGen 1000 IU
- Proceed with your next dose immediately and continue at regular intervals as advised by your doctor.
- **Do not** take a double dose to make up for a forgotten dose**.**

If you want to stop using Helixate NexGen 1000 IU
Do not stop using Helixate NexGen without consulting your doctor.

Documentation
It is recommended that every time that you use Helixate NexGen, the name and batch number of the product are documented.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most **serious** side effects are **hypersensitivity reactions** or anaphylactic shock (rare side effect). If allergic or anaphylactic reactions occur, the injection/infusion should be **stopped immediately**. **Please consult your doctor immediately**.

Overall list of possible side effects:

Very common:
may affect more than 1 in 10 users
- formation of neutralising antibodies to factor VIII (inhibitors) in previously untreated patients

Common:
may affect up to 1 in 10 users**:**
- rash/itchy rash
- local reactions where you injected the medication (e.g. burning sensation, temporary redness)

Uncommon
may affect up to 1 in 100 users
- formation of neutralising antibodies to factor VIII (inhibitors) in previously treated patients

Rare:
may affect up to 1 in 1,000 users
- hypersensitivity reactions including severe sudden allergic reaction (which may include hives, nausea, urticaria, angioedema, chills, flushing, headache, lethargy, wheezing or difficulty breathing, restlessness, tachycardia, tingling or anaphylactic shock, 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)
- fever

Not known:
frequency cannot be estimated from the available data
- dysgeusia

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.**

Antibodies (Inhibitors)
The formation of neutralising antibodies to factor VIII (inhibitors) is a known complication in the treatment of patients with haemophilia A. Your doctor may wish to carry out tests to monitor inhibitor development.

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

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Helixate NexGen 1000 IU

Keep this medicine out of the sight and reach 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.

Within the expiry date indicated on the label, this medicine when kept in its outer carton may be stored at ambient room temperature (up to 25°C) for a limited period of 12 months. In this case, this medicine expires at the end of this 12-month period or the expiration date on the product vial, whichever is earlier. The new expiry date must be noted on the outer carton.

Do not refrigerate the solution after reconstitution. The reconstituted solution must be used within 3 hours. This product is for single use only. Any unused solution must be discarded.

Do not use this medicine 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 this medicine if you notice any particles or the solution is cloudy.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Helixate NexGen 1000 IU contains

Powder
The **active** substance is human coagulation factor VIII (octocog alfa) produced by recombinant DNA technology.
The **other** ingredients are glycine, sodium chloride, calcium chloride, histidine, polysorbate 80, and sucrose (*see end of section 2)*.

Solvent
Water for injections, sterilised.

What Helixate NexGen 1000 IU looks like and content of the pack

Helixate NexGen 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 1000 IU.

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13342 Berlin
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Manufacturer
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This leaflet was last revised in {**MM/YYYY**}

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

Package Leaflet: Information for the user

Helixate NexGen 2000 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 because it contains important information for you.
- 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 only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Helixate NexGen 2000 IU is and what it is used for

Helixate NexGen 2000 IU contains the active substance human recombinant coagulation factor VIII (octocog alfa).

Helixate NexGen is used for treatment and prophylaxis of bleeding adults, adolescents and children of all ages with haemophilia A (congenital factor VIII deficiency).
This preparation does not contain von Willebrand factor and is therefore not to be used in von Willebrand's disease.

The vial contains a dry white to slightly yellow powder or cake, as well as water for injections to be used to reconstitute the contents of the vial.

The vial with powder contains 2000 IU (International Units) of octocog alfa. After reconstitution with the water for injection, each vial contains octocog alfa 400 IU/ml.

2. What you need to know before you use Helixate NexGen 2000 IU

Do not use Helixate NexGen 2000 IU
- If you are allergic to octocog alfa or to any of the other ingredients of this medicine *(listed in section 6 and end of section 2*).
- If you are allergic to mouse or hamster protein.

If you are unsure about this, ask your doctor.

Warnings and precautions
Talk to your doctor or pharmacist before using Helixate NexGen 2000 IU.

Take special care with Helixate NexGen 2000 IU

- If you experience tightness in the chest, feeling dizzy, feeling sick or faint, or experience dizziness on standing, you may be experiencing a rare severe sudden allergic reaction (a so-called anaphylactic reaction) to this medicine. If this occurs, **stop administering the product** immediately and seek medical advice.

- Your doctor may carry out tests to ensure that your current dose of this medicine provides adequate factor VIII levels.

- If your bleeding is not being controlled with your usual dose of this medicine, consult your doctor immediately. You may have developed factor VIII inhibitors and your doctor may carry out tests to confirm this. Factor VIII inhibitors are antibodies in the blood which block the factor VIII you are using, and makes it less effective to prevent and control 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.

- If you have been told you have heart disease or are at risk for heart disease, tell your doctor or pharmacist.

- If for the administration of Helixate NexGen you will require a central venous access device (CVAD), the risk of CVAD-related complications including local infections, bacteria in the blood (bacteremia) and the formation of a blood clot in the blood vessel (thrombosis) where the catheter is inserted should be considered by your doctor.

Other medicines and Helixate NexGen 2000 IU
Interactions with other medicines are not known. However, please tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Pregnancy, breast-feeding and fertility
Experience regarding fertility or the use of Helixate NexGen during pregnancy and breast-feeding is not available. Therefore, if you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.

Driving and using machines
No effects on ability to drive or use machines have been observed.

Helixate NexGen 2000 IU contains sodium
This medicinal product contains less than 23 mg sodium per vial, i.e. essentially “sodium-free”.

3. How to use Helixate NexGen 2000 IU

- Always use this medicine exactly as described in this leaflet or as your doctor or pharmacist have told you. Check with your doctor or pharmacist if you are not sure.

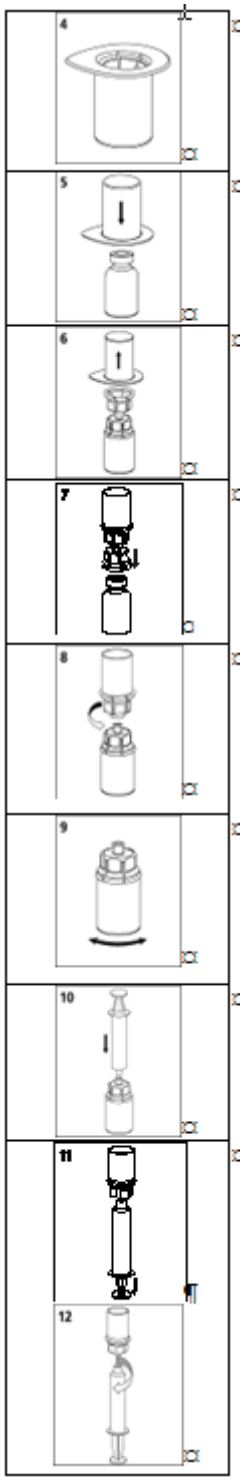
- This medicine is intended for intravenous administration only and should be administered within 3 hours after reconstitution.

- You must use aseptic conditions (meaning clean and germ free) during reconstitution and administration. Use only the medical devices for reconstitution and administration that are provided with each package of this medicine. If these components cannot be used, please contact your doctor. If any component of the package is opened or damaged, do not use it.

- You must filter the reconstituted product before administration to remove potential particulate matter in the solution. Filtering is achieved by using the Mix2Vial adapter.

- This medicine 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:

Reconstitution and administration



1. Wash your 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 solvent 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. Do **not** remove the Mix2Vial from the blister package!
5. Place the solvent vial on an even, clean surface and hold the vial tight. Take the Mix2Vial together with the blister package and push the spike of the blue adapter end **straight down** through the solvent vial stopper.
6. Carefully remove the blister package from the Mix2Vial set by holding at the rim, and pulling **vertically** upwards. Make sure that you only pull away the blister package and not the Mix2Vial set.
7. Place the product vial on an even and firm surface. Invert the solvent vial with the Mix2Vial set attached and push the spike of the transparent adapter end **straight down** through the product vial stopper. The solvent will automatically flow into the product vial.
8. With one hand grasp the product-side of the Mix2Vial set and with the other hand grasp the solvent-side and unscrew the set carefully into two pieces. Discard the solvent vial with the blue Mix2Vial adapter attached.
9. Gently swirl the product vial with the transparent adapter attached until the substance is fully dissolved. Do not shake. Inspect visually for particulate matter and discoloration prior to administration. Do not use solutions containing visible particles or that are cloudy.
10. Draw air into an empty, sterile syringe. While the product vial is upright, connect the syringe to the Mix2Vial´s Luer Lock fitting. Inject air into the product vial.
11. While keeping the syringe plunger pressed, turn the system upside down and draw the solution into the syringe by pulling the plunger back slowly.
12. Now that the solution has been transferred into the syringe, firmly hold on to the barrel of the syringe (keeping the syringe plunger facing down) and disconnect the transparent Mix2Vial adapter from the syringe. Hold the syringe upright and push the plunger until no air is left in the syringe.
13. Apply a tourniquet.
14. Determine the point of injection and prepare antiseptically.
15. Puncture the vein and secure the venipuncture set with a plaster.
16 Let blood flow back to the open end of the venipuncture set and then attach the syringe with the solution. Make sure that no blood enters the syringe.
17. Remove tourniquet.
18. Inject the solution intravenously over several minutes, keeping an eye on the position of the needle. The speed of administration should be based on the patient’s comfort, but should not be faster than 2ml/min maximum rate of infusion.
19. If a further dose needs to be administered, use a new syringe with product reconstituted as described above.

20. 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.

Treatment of bleeding
How much Helixate NexGen 2000 IU you should use and how often you should use it depends on many factors such as your weight, the severity of your haemophilia, where the bleed is and how serious it is, whether you have inhibitors and how high the inhibitor titre is and the factor VIII level that is needed.

Your doctor will calculate the dose of this medicine and how frequently you should use it to get the necessary level of factor VIII activity in your blood. He/she should always adjust the amount of this medicine to be administered and the frequency of administration according to your individual needs. Under certain circumstances larger amounts than those calculated may be required, especially for the initial dose.

Prevention of bleeding
If you are using Helixate NexGen to prevent bleeding (prophylaxis), your doctor will calculate the dose for you. This will usually be in the range of 20 to 40 IU of octocog alfa per kg of body weight, given every 2 to 3 days. However, in some cases, especially for younger patients, shorter dose intervals or higher doses may be necessary.

Laboratory tests
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. For major surgery in particular, close monitoring of the substitution therapy by means of coagulation analysis must be carried out.

If bleeding is not controlled
If the factor VIII level in your plasma fails to reach expected levels, or if bleeding is not controlled after apparently adequate dose, you may have developed factor VIII inhibitors. This must be checked by an experienced doctor.
If you have the impression that the effect of this medicine is too strong or too weak, talk to your doctor.

Patients with inhibitors
If you have been told by your doctor that you have developed factor VIII inhibitors you may need to use a larger amount of this medicine to control bleeding. If this dose does not control your bleeding your doctor may consider giving you an additional product, factor VIIa concentrate or (activated) prothrombin complex concentrate.
These treatments should be prescribed by doctors with experience in the care of patients with haemophilia A. Speak to your doctor if you would like further information on this.
Do not increase your dose of medicine you use to control your bleeding without consulting your doctor.

Speed of administration
This medicine 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).

Duration of treatment
Your doctor will tell you, how often and at what intervals this medicine is to be administered.

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

If you use more Helixate NexGen 2000 IU than you should
No cases of overdose with recombinant coagulation factor VIII have been reported.

If you have used more Helixate NexGen 2000 IU than you should, please inform your doctor.

If you forget to use Helixate NexGen 2000 IU
- Proceed with your next dose immediately and continue at regular intervals as advised by your doctor.
- **Do not** take a double dose to make up for a forgotten dose**.**

If you want to stop using Helixate NexGen 2000 IU
Do not stop using Helixate NexGen without consulting your doctor.

Documentation
It is recommended that every time that you use Helixate NexGen, the name and batch number of the product are documented.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most **serious** side effects are **hypersensitivity reactions** or anaphylactic shock (rare side effect). If allergic or anaphylactic reactions occur, the injection/infusion should be **stopped immediately**. **Please consult your doctor immediately**.

Overall list of possible side effects:

Very common:
may affect more than 1 in 10 users
- formation of neutralising antibodies to factor VIII (inhibitors) in previously untreated patients

Common:
may affect up to 1 in 10 users**:**
- rash/itchy rash
- local reactions where you injected the medication (e.g. burning sensation, temporary redness)

Uncommon
may affect up to 1 in 100 users
- formation of neutralising antibodies to factor VIII (inhibitors) in previously treated patients

Rare:
may affect up to 1 in 1,000 users
- hypersensitivity reactions including severe sudden allergic reaction (which may include hives, nausea, urticaria, angioedema, chills, flushing, headache, lethargy, wheezing or difficulty breathing, restlessness, tachycardia, tingling or anaphylactic shock, 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)
- fever

Not known:
frequency cannot be estimated from the available data
- dysgeusia

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.**

Antibodies (Inhibitors)
The formation of neutralising antibodies to factor VIII (inhibitors) is a known complication in the treatment of patients with haemophilia A. Your doctor may wish to carry out tests to monitor inhibitor development.

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

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Helixate NexGen 2000 IU

Keep this medicine out of the sight and reach 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.

Within the expiry date indicated on the label, this medicine when kept in its outer carton may be stored at ambient room temperature (up to 25°C) for a limited period of 12 months. In this case, this medicine expires at the end of this 12-month period or the expiration date on the product vial, whichever is earlier. The new expiry date must be noted on the outer carton.

Do not refrigerate the solution after reconstitution. The reconstituted solution must be used within 3 hours. This product is for single use only. Any unused solution must be discarded.

Do not use this medicine 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 this medicine if you notice any particles or the solution is cloudy.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Helixate NexGen 2000 IU contains

Powder
The **active** substance is human coagulation factor VIII (octocog alfa) produced by recombinant DNA technology.
The **other** ingredients are glycine, sodium chloride, calcium chloride, histidine, polysorbate 80, and sucrose (*see end of section 2)*.

Solvent
Water for injections, sterilised.

What Helixate NexGen 2000 IU looks like and content of the pack

Helixate NexGen 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 2000 IU.

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Bayer Pharma AG
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Manufacturer
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This leaflet was last revised in {**MM/YYYY**}

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

Package Leaflet: Information for the user

Helixate NexGen 3000 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 because it contains important information for you.
- 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 only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Helixate NexGen 3000 IU is and what it is used for

Helixate NexGen 3000 IU contains the active substance human recombinant coagulation factor VIII (octocog alfa).

Helixate NexGen is used for treatment and prophylaxis of bleeding adults, adolescents and children of all ages with haemophilia A (congenital factor VIII deficiency).
This preparation does not contain von Willebrand factor and is therefore not to be used in von Willebrand's disease.

The vial contains a dry white to slightly yellow powder or cake, as well as water for injections to be used to reconstitute the contents of the vial.

The vial with powder contains 3000 IU (International Units) of octocog alfa. After reconstitution with the water for injection, each vial contains octocog alfa 600 IU/ml.

2. What you need to know before you use Helixate NexGen 3000 IU

Do not use Helixate NexGen 3000 IU
- If you are allergic to octocog alfa or to any of the other ingredients of this medicine *(listed in section 6 and end of section 2*).
- If you are allergic to mouse or hamster protein.

If you are unsure about this, ask your doctor.

Warnings and precautions
Talk to your doctor or pharmacist before using Helixate NexGen 3000 IU.

Take special care with Helixate NexGen 3000 IU

- If you experience tightness in the chest, feeling dizzy, feeling sick or faint, or experience dizziness on standing, you may be experiencing a rare severe sudden allergic reaction (a so-called anaphylactic reaction) to this medicine. If this occurs, **stop administering the product** immediately and seek medical advice.

- Your doctor may carry out tests to ensure that your current dose of this medicine provides adequate factor VIII levels.

- If your bleeding is not being controlled with your usual dose of this medicine, consult your doctor immediately. You may have developed factor VIII inhibitors and your doctor may carry out tests to confirm this. Factor VIII inhibitors are antibodies in the blood which block the factor VIII you are using, and makes it less effective to prevent and control 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.

- If you have been told you have heart disease or are at risk for heart disease, tell your doctor or pharmacist.

- If for the administration of Helixate NexGen you will require a central venous access device (CVAD), the risk of CVAD-related complications including local infections, bacteria in the blood (bacteremia) and the formation of a blood clot in the blood vessel (thrombosis) where the catheter is inserted should be considered by your doctor.

Other medicines and Helixate NexGen 3000 IU
Interactions with other medicines are not known. However, please tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

Pregnancy, breast-feeding and fertility
Experience regarding fertility or the use of Helixate NexGen during pregnancy and breast-feeding is not available. Therefore, if you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.

Driving and using machines
No effects on ability to drive or use machines have been observed.

Helixate NexGen 3000 IU contains sodium
This medicinal product contains less than 23 mg sodium per vial, i.e. essentially “sodium-free”.

3. How to use Helixate NexGen 3000 IU

- Always use this medicine exactly as described in this leaflet or as your doctor or pharmacist have told you. Check with your doctor or pharmacist if you are not sure.

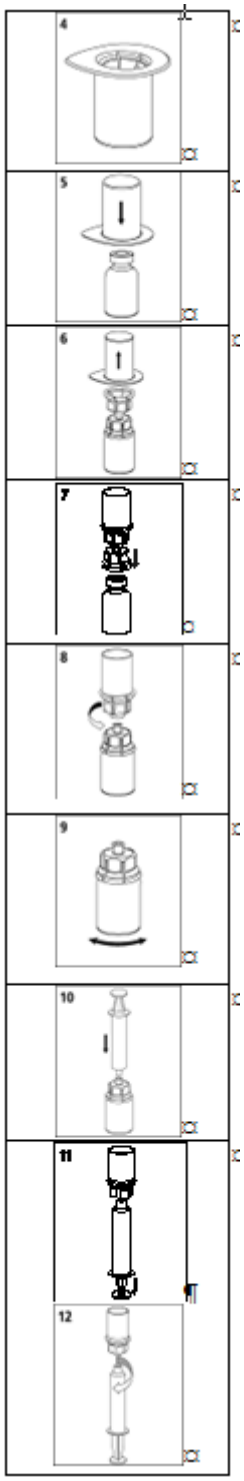
- This medicine is intended for intravenous administration only and should be administered within 3 hours after reconstitution.

- You must use aseptic conditions (meaning clean and germ free) during reconstitution and administration. Use only the medical devices for reconstitution and administration that are provided with each package of this medicine. If these components cannot be used, please contact your doctor. If any component of the package is opened or damaged, do not use it.

- You must filter the reconstituted product before administration to remove potential particulate matter in the solution. Filtering is achieved by using the Mix2Vial adapter.

- This medicine 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:

Reconstitution and administration



1. Wash your 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 solvent 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. Do **not** remove the Mix2Vial from the blister package!
5. Place the solvent vial on an even, clean surface and hold the vial tight. Take the Mix2Vial together with the blister package and push the spike of the blue adapter end **straight down** through the solvent vial stopper.
6. Carefully remove the blister package from the Mix2Vial set by holding at the rim, and pulling **vertically** upwards. Make sure that you only pull away the blister package and not the Mix2Vial set.
7. Place the product vial on an even and firm surface. Invert the solvent vial with the Mix2Vial set attached and push the spike of the transparent adapter end **straight down** through the product vial stopper. The solvent will automatically flow into the product vial.
8. With one hand grasp the product-side of the Mix2Vial set and with the other hand grasp the solvent-side and unscrew the set carefully into two pieces. Discard the solvent vial with the blue Mix2Vial adapter attached.
9. Gently swirl the product vial with the transparent adapter attached until the substance is fully dissolved. Do not shake. Inspect visually for particulate matter and discoloration prior to administration. Do not use solutions containing visible particles or that are cloudy.
10. Draw air into an empty, sterile syringe. While the product vial is upright, connect the syringe to the Mix2Vial´s Luer Lock fitting. Inject air into the product vial.
11. While keeping the syringe plunger pressed, turn the system upside down and draw the solution into the syringe by pulling the plunger back slowly.
12. Now that the solution has been transferred into the syringe, firmly hold on to the barrel of the syringe (keeping the syringe plunger facing down) and disconnect the transparent Mix2Vial adapter from the syringe. Hold the syringe upright and push the plunger until no air is left in the syringe.
13. Apply a tourniquet.
14. Determine the point of injection and prepare antiseptically.
15. Puncture the vein and secure the venipuncture set with a plaster.
16 Let blood flow back to the open end of the venipuncture set and then attach the syringe with the solution. Make sure that no blood enters the syringe.
17. Remove tourniquet.
18. Inject the solution intravenously over several minutes, keeping an eye on the position of the needle. The speed of administration should be based on the patient’s comfort, but should not be faster than 2ml/min maximum rate of infusion.
19. If a further dose needs to be administered, use a new syringe with product reconstituted as described above.

20. 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.

Treatment of bleeding
How much Helixate NexGen 3000 IU you should use and how often you should use it depends on many factors such as your weight, the severity of your haemophilia, where the bleed is and how serious it is, whether you have inhibitors and how high the inhibitor titre is and the factor VIII level that is needed.

Your doctor will calculate the dose of this medicine and how frequently you should use it to get the necessary level of factor VIII activity in your blood. He/she should always adjust the amount of this medicine to be administered and the frequency of administration according to your individual needs. Under certain circumstances larger amounts than those calculated may be required, especially for the initial dose.

Prevention of bleeding
If you are using Helixate NexGen to prevent bleeding (prophylaxis), your doctor will calculate the dose for you. This will usually be in the range of 20 to 40 IU of octocog alfa per kg of body weight, given every 2 to 3 days. However, in some cases, especially for younger patients, shorter dose intervals or higher doses may be necessary.

Laboratory tests
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. For major surgery in particular, close monitoring of the substitution therapy by means of coagulation analysis must be carried out.

If bleeding is not controlled
If the factor VIII level in your plasma fails to reach expected levels, or if bleeding is not controlled after apparently adequate dose, you may have developed factor VIII inhibitors. This must be checked by an experienced doctor.
If you have the impression that the effect of this medicine is too strong or too weak, talk to your doctor.

Patients with inhibitors
If you have been told by your doctor that you have developed factor VIII inhibitors you may need to use a larger amount of this medicine to control bleeding. If this dose does not control your bleeding your doctor may consider giving you an additional product, factor VIIa concentrate or (activated) prothrombin complex concentrate.
These treatments should be prescribed by doctors with experience in the care of patients with haemophilia A. Speak to your doctor if you would like further information on this.
Do not increase your dose of medicine you use to control your bleeding without consulting your doctor.

Speed of administration
This medicine 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).

Duration of treatment
Your doctor will tell you, how often and at what intervals this medicine is to be administered.

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

If you use more Helixate NexGen 3000 IU than you should
No cases of overdose with recombinant coagulation factor VIII have been reported.

If you have used more Helixate NexGen 3000 IU than you should, please inform your doctor.

If you forget to use Helixate NexGen 3000 IU
- Proceed with your next dose immediately and continue at regular intervals as advised by your doctor.
- **Do not** take a double dose to make up for a forgotten dose**.**

If you want to stop using Helixate NexGen 3000 IU
Do not stop using Helixate NexGen without consulting your doctor.

Documentation
It is recommended that every time that you use Helixate NexGen, the name and batch number of the product are documented.

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

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The most **serious** side effects are **hypersensitivity reactions** or anaphylactic shock (rare side effect). If allergic or anaphylactic reactions occur, the injection/infusion should be **stopped immediately**. **Please consult your doctor immediately**.

Overall list of possible side effects:

Very common:
may affect more than 1 in 10 users
- formation of neutralising antibodies to factor VIII (inhibitors) in previously untreated patients

Common:
may affect up to 1 in 10 users**:**
- rash/itchy rash
- local reactions where you injected the medication (e.g. burning sensation, temporary redness)

Uncommon
may affect up to 1 in 100 users
- formation of neutralising antibodies to factor VIII (inhibitors) in previously treated patients

Rare:
may affect up to 1 in 1,000 users
- hypersensitivity reactions including severe sudden allergic reaction (which may include hives, nausea, urticaria, angioedema, chills, flushing, headache, lethargy, wheezing or difficulty breathing, restlessness, tachycardia, tingling or anaphylactic shock, 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)
- fever

Not known:
frequency cannot be estimated from the available data
- dysgeusia

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.**

Antibodies (Inhibitors)
The formation of neutralising antibodies to factor VIII (inhibitors) is a known complication in the treatment of patients with haemophilia A. Your doctor may wish to carry out tests to monitor inhibitor development.

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

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Helixate NexGen 3000 IU

Keep this medicine out of the sight and reach 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.

Within the expiry date indicated on the label, this medicine when kept in its outer carton may be stored at ambient room temperature (up to 25°C) for a limited period of 12 months. In this case, this medicine expires at the end of this 12-month period or the expiration date on the product vial, whichever is earlier. The new expiry date must be noted on the outer carton.

Do not refrigerate the solution after reconstitution. The reconstituted solution must be used within 3 hours. This product is for single use only. Any unused solution must be discarded.

Do not use this medicine 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 this medicine if you notice any particles or the solution is cloudy.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Helixate NexGen 3000 IU contains

Powder
The **active** substance is human coagulation factor VIII (octocog alfa) produced by recombinant DNA technology.
The **other** ingredients are glycine, sodium chloride, calcium chloride, histidine, polysorbate 80, and sucrose (*see end of section 2)*.

Solvent
Water for injections, sterilised.

What Helixate NexGen 3000 IU looks like and content of the pack

Helixate NexGen 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 3000 IU.

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Manufacturer
Bayer HealthCare Manufacturing S.r.l.
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Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu