ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Helixate NexGen 250 IU powder and solvent for solution for injection
Helixate NexGen 500 IU powder and solvent for solution for injection
Helixate NexGen 1000 IU powder and solvent for solution for injection
Helixate NexGen 2000 IU powder and solvent for solution for injection
Helixate NexGen 3000 IU powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains nominally 250/500/1000/2000/3000 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.

- One mL Helixate NexGen 250 IU contains approximately 100 IU (250 IU / 2.5 mL) of recombinant human coagulation factor VIII (INN: octocog alfa) after reconstitution with water for injections.
- One mL Helixate NexGen 500 IU contains approximately 200 IU (500 IU / 2.5 mL) of recombinant human coagulation factor VIII (INN: octocog alfa) after reconstitution with water for injections.
- One mL Helixate NexGen 1000 IU contains approximately 400 IU (1000 IU / 2.5 mL) of recombinant human coagulation factor VIII (INN: octocog alfa) after reconstitution with water for injections.
- One mL Helixate NexGen 2000 IU contains approximately 400 IU (2000 IU / 5 mL) of recombinant human coagulation factor VIII (INN: octocog alfa) after reconstitution with water for injections.
- One mL Helixate NexGen 3000 IU contains approximately 600 IU (3000 IU / 5 mL) of recombinant human coagulation factor VIII (INN: octocog alfa) after reconstitution with water for injections.

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.

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.

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:

Table 1: Guide for dosing in bleeding episodes and surgery

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.

Special populations

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 2 to 5 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).

Table 2: 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 severity of the disease as well as the exposure to factor VIII, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days.

Cases of recurrent inhibitor (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 previous history of inhibitor development. Therefore, it is recommended to monitor all patients carefully for inhibitor occurrence following any product switch.

The clinical relevance of inhibitor development will depend on the titre of the inhibitor, with low titre inhibitors which are transiently present or remain consistently low titre posing less risk of insufficient clinical response than high titre inhibitors.

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 factor VIII inhibitor presence 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 disease 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.

Development of neutralising antibodies (inhibitors) may occur in patients with haemophilia A treated with factor VIII, including with Helixate NexGen. If such inhibitors occur, the condition will 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).

Table 3: Frequency of adverse drug reactions

MedDRA Standard System Organ Class	Frequency				
	Very common	**Common**	**Uncommon**	**Rare**	**Very Rare / not known**
Blood and the Lymphatic System Disorders	FVIII Inhibition (PUPs)*		FVIII Inhibition (PTPs)*		
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

* Frequency is based on studies with all FVIII products which included patients with severe haemophilia A. PTPs = previously-treated patients. PUPs = previously-untreated patients

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.

The reconstituted medicinal product is a clear and colourless solution.
Helixate NexGen powder should only be reconstituted with the supplied solvent (2.5 mL (for 250 IU, 500 IU and 1000 IU) or 5 mL (for 2000 IU and 3000 IU) 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 medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/144/001 - Helixate NexGen 250 IU
EU/1/00/144/002 - Helixate NexGen 500 IU
EU/1/00/144/003 - Helixate NexGen 1000 IU
EU/1/00/144/004 - Helixate NexGen 2000 IU
EU/1/00/144/005 - Helixate NexGen 3000 IU

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 MANUFACTURER RESPONSIBLE 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.

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
Helixate NexGen 500 IU powder and solvent for solution for injection
Helixate NexGen 1000 IU powder and solvent for solution for injection
Helixate NexGen 2000 IU powder and solvent for solution for injection
Helixate NexGen 3000 IU powder and solvent for solution for injection

Recombinant coagulation factor VIII (octocog alfa)

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Helixate NexGen 250 IU contains (250 IU / 2.5 mL) = 100 IU octocog alfa per mL after reconstitution.
Helixate NexGen 500 IU contains (500 IU / 2.5 mL) = 200 IU octocog alfa per mL after reconstitution.
Helixate NexGen 1000 IU contains (1000 IU / 2.5 mL) = 400 IU octocog alfa per mL after reconstitution.
Helixate NexGen 2000 IU contains (2000 IU / 5 mL) = 400 IU octocog alfa per mL after reconstitution.
Helixate NexGen 3000 IU contains (3000 IU / 5 mL) = 600 IU octocog alfa per 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.
1 vial with 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 AG
51368 Leverkusen
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/144/001 - Helixate NexGen 250 IU
EU/1/00/144/002 - Helixate NexGen 500 IU
EU/1/00/144/003 - Helixate NexGen 1000 IU
EU/1/00/144/004 - Helixate NexGen 2000 IU
EU/1/00/144/005 - Helixate NexGen 3000 IU

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Helixate NexGen 250
Helixate NexGen 500
Helixate NexGen 1000
Helixate NexGen 2000
Helixate NexGen 3000

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

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
Helixate NexGen 500 IU powder for solution for injection
Helixate NexGen 1000 IU powder for solution for injection
Helixate NexGen 2000 IU powder for solution for injection
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

250 IU (octocog alfa) (500 IU/mL after reconstitution).
500 IU (octocog alfa) (200 IU/mL after reconstitution).
1000 IU (octocog alfa) (400 IU/mL after reconstitution).
2000 IU (octocog alfa) (400 IU/mL after reconstitution).
3000 IU (octocog alfa) (600 IU/mL after reconstitution).

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL WITH 2.5 mL or 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 [for reconstitution of strengths 250/500/1000 IU]
5 mL [for reconstitution of strengths 2000/3000 IU]

6. OTHER

B. PACKAGE LEAFLET

Package Leaflet: Information for the user

Helixate NexGen 250 IU powder and solvent for solution for injection
Helixate NexGen 500 IU powder and solvent for solution for injection
Helixate NexGen 1000 IU powder and solvent for solution for injection
Helixate NexGen 2000 IU powder and solvent for solution for injection
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 is and what it is used for

Helixate NexGencontains 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.

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

Do not use Helixate NexGen
- 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
Take special care with Helixate NexGen and talk to your doctor or pharmacist 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 bleeding is not being controlled with your usual dose of this medicine. The formation of inhibitors (antibodies) is a known complication that can occur during treatment with all Factor VIII medicines. These inhibitors, especially at high levels, stop the treatment working properly and you or your child will be monitored carefully for the development of these inhibitors. If your or your child's bleeding is not being controlled with Helixate NexGen, tell your doctor immediately.
- you have previously developed a factor VIII inhibitor and you switch factor VIII products, you may be at risk of your inhibitor coming back.
- you have been told you have heart disease or are at risk for heart disease.
- you require a central venous access device (CVAD) for the administration of Helixate NexGen. You may be at 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.

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

Other medicines and Helixate NexGen
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.

Children and adolescents
The listed warnings and precautions apply to patients of all ages, adults and children.

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.
Helixate NexGen is not likely to affect the fertility in male or female patients, as the active substance is naturally occurring in the body.

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

Helixate NexGen contains sodium
This medicinal product contains less than 1 mmol (23 mg) sodium per vial and is therefore considered essentially "sodium-free".

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

3. How to use Helixate NexGen

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

Treatment of bleeding
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. The doctor should always adjust the dose and the frequency of administration according to your individual needs. How much Helixate NexGen 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
- the factor VIII level that is needed.

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.

Use in children and adolescents
Helixate NexGen can be used in children of all ages.

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.

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.

How Helixate NexGen is given

This medicine is intended for injection into a vein over 2 to 5 minutes depending on the total volume and your comfort level and should be used within 3 hours after preparing the solution.

How Helixate NexGen is prepared for administration
Use only the items 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 any possible particles in the solution. **You are filtering** 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 **detailed instructions for reconstitution and administration provided at the end of this leaflet.**

If you use more Helixate NexGen than you should
No cases of overdose with recombinant coagulation factor VIII have been reported.
If you have used more Helixate NexGen than you should, please inform your doctor.

If you forget to use Helixate NexGen
- 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
Do not stop using Helixate NexGen without consulting your doctor.

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**.

For children not previously treated with Factor VIII medicines, inhibitor antibodies (see section 2) may form very commonly (more than 1 in 10 patients); however patients who have received previous treatment with Factor VIII (more than 150 days of treatment) the risk is uncommon (less than 1 in 100 patients). If this happens your or your child's medicines may stop working properly and you or your child may experience persistent bleeding. If this happens, you should contact your doctor immediately.

Other possible side effects:

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)

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 (strange taste)

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.**

Hypersensitivity reactions
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

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 contains

Powder
The **active** substance is human coagulation factor VIII (octocog alfa) produced by recombinant DNA technology. Each vial of Helixate NexGen contains nominally 250, 500, 1000, 2000 or 3000 IU octocog alfa.
The **other** ingredients are glycine, sodium chloride, calcium chloride, histidine, polysorbate 80, and sucrose (see end of section 2).

Solvent
Water for injections

What Helixate NexGen 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 this medicine.

Marketing Authorisation Holder
Bayer AG
51368 Leverkusen
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.

België/Belgique/Belgien
CSL Behring N.V.
Tél/Tel: +32-(0)15 28 89 20
България
Novimed Ltd.
Тел. + 359 2 850 86 17
Česká republika
CSL Behring s.r.o.
Tel: + 420 702 137 233
Danmark
CSL Behring AB
Tlf: +46-(0)8-54496670
Deutschland
CSL Behring GmbH
Tel: +49-(0)69-30584437
Eesti
CSL Behring GmbH
Tel: +49-(0)69-30584437
Ελλάδα
CSL Behring ΕΠΕ,
Τηλ: +30-210 7255 660
España
CSL Behring, S. A.
Tel: +34 93 367 1870
France
CSL Behring S.A.
Tél: +33-(0)1-53585400
Hrvatska
PharmaSwiss d.o.o.
Tel: +385 (1) 631-1833
Ireland
CSL Behring UK Limited
Tel: +44-(0)1444 447405
Ísland
CSL Behring AB
Simi: +46-(0)8-54496670
Italia
CSL Behring S.p.A.
Tel: +39-02-34964200
Κύπρος
CSL Behring ΕΠΕ,
Τηλ: +30-210 7255 660
Latvija
CSL Behring GmbH
Tel: +49-(0)69-30584437
Lietuva
CSL Behring GmbH
Tel: +49-(0)69-30584437
Luxembourg/Luxemburg
CSL Behring N.V.
Tél/Tel: +32-(0)15 28 89 20
Magyarország
CSL Behring KFT
Tel: +36-1-213 4290
Malta
AM Mangion Ltd.
Tel: +356 2397 6333
Nederland
CSL Behring BV
Tel: +31-(0) 85 111 96 00
Norge
CSL Behring AB
Tlf: +46-(0)8-54496670
Österreich
CSL Behring GmbH
Tel: +43-(0)1-20101-2463
Polska
CSL Behring sp. z o.o.
Tel. +48 22 213 22 65
Portugal
CSL Behring, Lda.
Tel. +351-21-7826230
România
Prisum International Trading srl
Tel. +40 21 322 01 71
Slovenija
MediSanus d.o.o.
Tel: +386 1 25 71 496
Slovenská republika
CSL Behring s.r.o.
Tel: +421 911 653 862
Suomi/Finland
CSL Behring AB
Puh/Tel: +46-(0)8-54496670
Sverige
CSL Behring AB
Tel: +46-(0)8-54496670
United Kingdom
CSL Behring UK Limited
Tel: +44-(0)1444 447405

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

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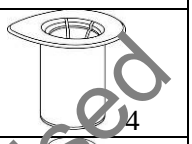
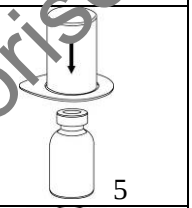
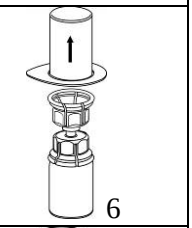
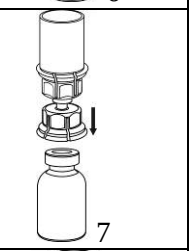
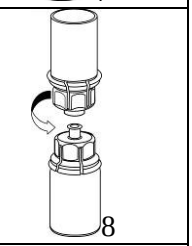
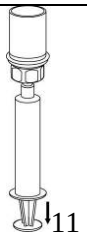
Detailed instructions for reconstitution and administration of Helixate NexGen using the Mix2Vial adapter:

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 antiseptic 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!	 4
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.	 5
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.	 6
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.	 7
8.	With one hand grasp the product side of the Mix2Vial set and with the other hand grasp the solvent-side and unscrew counter clockwise the set carefully into two pieces. Discard the solvent vial with the blue Mix2Vial adapter attached.	 8
9.	Gently swirl the product vial with the transparent adapter attached until the substance is fully dissolved. Do not shake. Carefully check for particles and discoloration before administration. Do not use solutions containing visible particles or that are cloudy.	 9
10.	Draw air into an empty, sterile syringe. While the product vial is upright, connect the syringe to the Mix2Vial´s Luer Lock fitting by screwing clockwise. Inject air into the product vial.	 10

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 by unscrewing counter clockwise. Hold the syringe upright and push the plunger until no air is left in the syringe.	
13.	Apply a tourniquet to your arm.	
14.	Determine the point of injection and clean the skin with an alcohol swab.	
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 into a vein over 2 to 5 minutes, keeping an eye on the position of the needle. The speed of injection should be based on your comfort, but should not be faster than 2.0 mL per minute.	
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 pad firmly over the injection site on your outstretched arm for about 2 minutes. Finally, apply a small pressure dressing to the injection site and consider if a plaster is necessary.	

Annex IV

Scientific conclusions

Scientific conclusions

Treatment of congenital haemophilia is currently based on prophylactic or on-demand replacement therapy with coagulation factor VIII (FVIII). FVIII replacement therapy can be generally categorised into two broad classes of products; plasma derived (pdFVIII) and recombinant (rFVIII) FVIII. A wide range of individual pdFVIII and rFVIII products are authorised for use in the European Union.

A major complication of FVIII therapy is the occurrence of IgG alloantibodies (inhibitors) that neutralise FVIII activity, causing loss of bleeding control. Treatment of patients who have developed inhibitors requires careful individual management and can be resistant to therapy.

Treatment with both pdFVIII and rFVIII can lead to development of inhibitors (tested with the Nijmegen method of the Bethesda assay and defined as ≥ 0.6 Bethesda units (BU) for "a low-titre" inhibitor and >5 BU for a "high-titre" inhibitor).

The occurrence of inhibitor development in haemophilia A patients receiving FVIII products mostly occurs in previously-untreated patients (PUPs) or minimally treated patients (MTPs) who are still within the first 50 days of exposure (EDs) to the treatment. Inhibitors are less likely to occur in previously-treated patients (PTPs).

The known risk factors for inhibitor development can be grouped into patient and treatment-related factors:

- Patient-related risk factors include type of F8 gene mutation, severity of haemophilia, ethnicity, family history of inhibitor development and possibly HLA-DR (Human Leukocyte Antigen - antigen D Related) constitution.
- Treatment-related factors include intensity of exposure, number of exposure days (EDs), on demand treatment posing a greater risk than prophylaxis, particularly in the context of danger signals such as trauma or surgery, and young age at first treatment poses a higher risk.

Whether there are significant differences in the risk of inhibitor development between different types of FVIII replacement product remains an area of uncertainty. Differences between products in each FVIII class and consequently differential risks between individual products, are biologically plausible. The pdFVIII class consists of products with or without Von Willebrand Factor (VWF), and those with VWF contain a range of VWF levels. Some experimental studies have suggested a role for VWF in protecting FVIII epitopes from recognition by the antigen-presenting cells, thereby reducing immunogenicity, although this remains theoretical. VWF is not present in rFVIII, but there is significant heterogeneity within the rFVIII class for instance due to the different manufacturing processes used, with a wide range of products from different manufacturers produced over the past 20 years. These different manufacturing processes (including the different cell lines used to engineer the rFVIII products) can in theory lead to differential immunogenicity.

In May 2016, an open-label, randomised controlled trial aimed at addressing the incidence of inhibitors between the two classes (pdFVIII vs. rFVIII products) was published in the New England Journal of Medicine[1]. This trial, known as the SIPPET study ("Survey of Inhibitors in Plasma-Product Exposed Toddlers") was conducted to evaluate the relative risk of inhibitors in patients treated with pdFVIII compared to rFVIII. It found that patients treated with rFVIII products had an 87% higher incidence of all inhibitors than those treated with pdFVIII (which contained VWF) (hazard ratio, 1.87; 95% CI, 1.17 to 2.96).

[1] F. Peyvandi et al. "A Randomized Trial of Factor VIII and Neutralizing Antibodies in Hemophilia A" N Engl J Med. 2016 May 26;374(21):2054-64)

On 6 July 2016 Paul-Ehrlich-Institut Germany initiated a referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, and requested the PRAC to assess the potential impact of the results of the SIPPET study on the marketing authorisations of relevant FVIII products and to issue a recommendation on whether these should be maintained, varied, suspended or revoked and whether any risk minimisation measures should be implemented. The referral focuses on the risk of inhibitor development in PUPs.

Further to the recent publication on the SIPPET study, the MAHs were requested to assess the potential impact of the results of this study and other relevant safety data on inhibitor development in PUPs on the MA of their FVIII product including consideration on risk minimisation measures.

The lead authors of the SIPPET study were also invited to respond to a list of questions regarding the study methods and findings and to present their conclusions at the February 2017 PRAC plenary meeting. Information submitted by the lead authors of the SIPPET study during the course of the referral was also taken into consideration by PRAC in reaching its conclusion.

Clinical discussion

Published observational studies

The responses of MAHs referred to a range of published observational studies (the CANAL, RODIN, FranceCoag, UKHCDO, amongst others) which have sought to evaluate any differential risks of inhibitor development between the classes of pdFVIII and rFVIII, as well as any differential risk of inhibitor development between products within the rFVIII class.

These studies have yielded different results and suffer from the limitations of observational studies, and in particular from possible selection bias. The risk of inhibitor development is multifactorial (aside from any putative product-specific risk), and such studies have not always been able to collect information on relevant covariates and to adjust the analyses accordingly; residual confounding is inevitably a significant uncertainty. Furthermore, over time there have been changes in manufacturing process of individual products and changes in treatment regimens between centres, hence "like for like" comparisons between products is not always possible. These factors make control of such studies and interpretation of the results challenging.

The CANAL study[2] found no evidence of a class difference, including pdFVIII products with considerable quantities of von Willebrand factor; for 'clinically relevant' inhibitors the adjusted hazard ratio was 0.7 (95% CI 0.4-1.1), and for high titre inhibitors (≥5 BU) was 0.8 (95% CI 0.4-1.3).

The RODIN/Pednet study[3] also found no evidence of a class difference in inhibitor risk between all pdFVIII vs all rFVIII; for 'clinically relevant' inhibitors the adjusted hazard ratio was 0.96 (95% CI 0.62-1.49), and for high titre inhibitors (≥5 BU/ml) was 0.95 (95% CI 0.56-1.61). However, the study found evidence of an increased risk of inhibitors (all and high titre) for 2nd generation rFVIII octocog alfa (Kogenate FS/Helixate NexGen) compared with 3rd generation rFVIII octocog alfa (which was driven solely by data for Advate).

Similar to RODIN/Pednet, the UKHCDO study found a significant increased risk of inhibitors (all and high titre) for Kogenate FS/Helixate NexGen (2nd generation rFVIII) compared to Advate (3rd generation rFVIII). Although this became non-significant when UK patients (also included in the RODIN/Pednet study were excluded. There was also evidence for an increased risk with Refacto AF (another 3rd generation rFVIII) vs Advate, but only for all inhibitor development. Like the UKHCDO

[2] http://www.bloodjournal.org/content/109/11/4648.full.pdf
[3] Gouw SC et al. PedNet and RODIN Study Group. Factor VIII products and inhibitor development in severe hemophilia A. N Engl J Med 2013; 368: 231-9. - http://www.bloodjournal.org/content/121/20/4046.full.pdf

study, the FranceCoag study also found no statistically significant increased risk for any rFVIII products vs Advate when French patients (also in the RODIN/Pednet study) were excluded.

Prior to the current referral, it was noted that PRAC had already considered the implications of the RODIN/Pednet, the UKHCDO and the FranceCoag studies for the EU marketing authorisations for FVIII products. In 2013, PRAC had concluded that the RODIN/Pednet findings were not sufficiently robust to support a conclusion that Kogenate FS/Helixate NexGen was associated with an increased risk of developing factor VIII inhibitors compared with other products. In 2016, PRAC had considered the findings of meta-analysis of all three studies (RODIN/Pednet, UKHCDO and FranceCoag studies), and again concluded that the currently available evidence does not confirm that Kogenate Bayer/Helixate NexGen is associated with an increased risk of factor VIII inhibitors, compared with other recombinant factor VIII products in PUPs.

MAH-sponsored studies

The MAHs provided an analysis of low and high titre inhibitor development in PUPs with severe haemophilia A (FVIII < 1%) from all clinical trials and observational studies conducted with their products, along with critical discussion on the limitations of these studies.

The data came from a very wide range of heterogenous studies across products and over time. Many of these studies were small and not specifically designed to evaluate the inhibitor risk in PUPs with severe haemophilia A. The studies were mostly single arm and do not provide data to perform comparative analysis (either between pdFVIII and rFVIII as a class comparison, or within the rFVIII class). However, the general estimates of inhibitor rates from these studies for individual products are broadly in line with the findings from large observational studies.

Of the larger and more relevant studies for pdFVIII products, inhibitor rates observed (often not stated if high or low titre) ranged from 3.5 to 33%, with most around 10-25%. However, in many cases little information was provided on the methods, patient populations and nature of the inhibitors to assess the information in the context of more recent published data. For most rFVIII products, newer and more relevant information from clinical trials in PUPs is available. Inhibitor rates in these studies range from 15 to 38% for all inhibitors and 9 to 22.6% for high titre inhibitors; i.e. within the range of 'very common'.

The PRAC also considered interim results submitted by the MAHs from ongoing studies from CSL (CRD019_5001) and Bayer (Leopold KIDS, 13400, part B.).

Furthermore, the PRAC examined clinical trials and the scientific literature for *de novo* inhibitors in PTPs. The analysis demonstrated that the frequency of inhibitor development is much lower in PTPs compared to PUPs. The available data showed that in many studies including the EUHASS registry (Iorio A, 2017[4]; Fischer K, 2015[5]) the frequency could be classified as "uncommon".

The SIPPET study

The SIPPET study was an open-label, randomized, multi-centre, multi-national trial investigating the incidence of neutralising allo-antibodies in patients with severe congenital haemophilia A (plasma FVIII concentration<1%) with either the use of pdFVIII or rFVIII concentrates. Eligible

[4] Iorio A, Barbara AM, Makris M, Fischer K, Castaman G, Catarino C, Gilman E, Kavakli K, Lambert T, Lassila R, Lissitchkov T, Mauser-Bunschoten E, Mingot-Castellano ME0, Ozdemir N1, Pabinger I, Parra R1, Pasi J, Peerlinck K, Rauch A6, Roussel-Robert V, Serban M, Tagliaferri A, Windyga J, Zanon E: Natural history and clinical characteristics of inhibitors in previously treated haemophilia A patients: a case series. Haemophilia. 2017 Mar;23(2):255-263. doi: 10.1111/hae.13167. Epub 2017 Feb 15.

[5] Fischer K, Lassila R, Peyvandi F, Calizzani G, Gatt A, Lambert T, Windyga J, Iorio A, Gilman E, Makris M; EUHASS participants Inhibitor development in haemophilia according to concentrate. Four-year results from the European HAemophilia Safety Surveillance (EUHASS) project. Thromb Haemost. 2015 May;113(5):968-75. doi: 10.1160/TH14-10-0826. Epub 2015 Jan 8.

patients (<6 years, male, severe haemophilia A, no previous treatment with any FVIII concentrate or only minimal treatment with blood components) were included from 42 sites. The primary and secondary outcomes assessed in the study were the incidence of all inhibitors (≥0.4 BU/ml) and the incidence of high-titre inhibitors (≥5 BU/ml), respectively.

Inhibitors developed in 76 patients, 50 of whom had high-titre inhibitors (≥5 BU). Inhibitors developed in 29 of the 125 patients treated with pdFVIII (20 patients had high-titre inhibitors) and in 47 of the 126 patients treated with rFVIII (30 patients had high-titre inhibitors). The cumulative incidence of all inhibitors was 26.8% (95% confidence interval [CI], 18.4 to 35.2) with pdFVIII and 44.5% (95% CI, 34.7 to 54.3) with rFVIII; the cumulative incidence of high-titre inhibitors was 18.6% (95% CI, 11.2 to 26.0) and 28.4% (95% CI, 19.6 to 37.2), respectively. In Cox regression models for the primary end point of all inhibitors, rFVIII was associated with an 87% higher incidence than pdFVIII (hazard ratio, 1.87; 95% CI, 1.17 to 2.96). This association was consistently observed in multivariable analysis. For high-titre inhibitors, the hazard ratio was 1.69 (95% CI, 0.96 to 2.98).

Ad hoc expert group meeting

The PRAC considered the views expressed by experts during an ad-hoc meeting. The expert group was of the view that the relevant available data sources have been considered. The expert group suggested that further data are needed to establish if there are clinically relevant differences in frequency of inhibitor development between different factor VIII products and that, in principle, such data should be collected separately for individual products, as degree of immunogenicity will be difficult to generalise across the classes of products (i.e. recombinant vs. plasma-derived).

The experts also agreed that the degree of immunogenicity of different products was adequately described overall with the amendments to the SmPC proposed by the PRAC highlighting the clinical relevance of inhibitor development (in particular low compared to high titre inhibitors), as well as the frequency of 'very common' in PUPs and 'uncommon' in PTPs. The experts also suggested studies which could further characterise the immunogenic properties of the factor VIII medicinal products (e.g. mechanistic, observational studies).

Discussion

The PRAC considered that as a prospective randomised trial, the SIPPET study avoided many of the design limitations of the observational and registry-based studies undertaken so far to evaluate the risk of inhibitor development in PUPs. However the PRAC is of the view that there are uncertainties with regards to the findings of the SIPPET study which preclude the conclusion that there is a higher risk of inhibitor development in PUPs treated with rFVIII products than pdFVIII products studied in this clinical trial, as detailed below:

- The SIPPET analysis does not allow for product-specific conclusions to be made as it relates only to a small number of certain FVIII products. The study was not designed and powered to generate sufficient product-specific data and, therefore, to draw any conclusions on the risk of inhibitor development for individual products. In particular, only 13 patients (10% of the FVIII arm) received a third generation rFVIII product. However, despite the lack of robust evidence to support differential risks between rFVIII products, differential risks cannot be excluded, as this is a heterogeneous product class with differences in composition and formulations. Therefore, there is a high degree of uncertainty around extrapolating the SIPPET findings to the entire rFVIII class, particularly for more recently-authorised rFVIII products which were not included in the SIPPET trial.
- The SIPPET study has methodological limitations, with particular uncertainty around whether the randomisation process (block size of 2) may have introduced a selection bias in the study.

- There were also deviations from the final protocol and statistical analysis plan. The statistical concerns include the fact that no pre-specified primary analysis has been published and the fact that the study was stopped early following the publication of the RODIN study indicating that Kogenate FS might be associated with an increased risk of inhibitor formation. Although this could not have been prevented, an early termination of an open label trial raises the possibility of investigator bias and inflation of the probability of detecting an effect that is not present.

- Treatment regimens in EU are different from those in the SIPPET study. The relevance for clinical practice in the EU (and therefore for the products subject to this procedure) is therefore questioned. It is uncertain whether the findings of SIPPET can be extrapolated to the risk of inhibitors in PUPs in current clinical practice in the EU as treatment modality and intensity have been suggested as risk factors for inhibitor development in previous studies. Importantly, the EU SmPCs do not include modified prophylaxis (as defined in the SIPPET study) as an authorised posology, and the impact of the apparent imbalance in the unspecified other combinations of treatment modality on the SIPPET findings is unclear. Therefore, it remains uncertain whether the same differential risk of inhibitor development observed in the SIPPET study would be apparent in patient populations treated in routine care in other countries where the modality of treatment (i.e. primary prophylaxis) is different from that in the study. The additional points of clarification provided by the SIPPET authors do not fully resolve this uncertainty.

Having considered the abovementioned results from SIPPET, the published literature and all the information submitted by the MAHs, as well as the views expressed by experts expressed at the *ad-hoc* expert meeting, the PRAC concluded that:

- Inhibitor development is an identified risk with both pdFVIII and rFVIII products. Although the clinical studies for some individual products have identified limited numbers of cases of inhibitor development, these tend to be small studies with methodological limitations, or studies not adequately designed to evaluate this risk.

- The FVIII products are heterogeneous, and the plausibility of different rates of inhibitor development between individual products cannot be excluded.

- Individual studies have identified a wide range of inhibitor development across products, but the direct comparability of study results is questionable based on diversity of study methods and patient populations over time.

- The SIPPET study was not designed to evaluate the risk of inhibitor development for individual products, and included a limited number of FVIII products. Due to heterogeneity across products, there is considerable uncertainty in extrapolating the findings of studies that have evaluated only class effects to individual products; and particularly to products (including more recently authorised products) which are not included in such studies.

- Finally, the PRAC noted that to date most studies evaluating a differential risk of inhibitor development between classes of FVIII products suffer from a variety of potential methodological limitations and based on the available data considered there is no clear and consistent evidence to suggest differences in relative risk between classes of FVIII products. Specifically, the findings from the SIPPET study, as well as those from the individual clinical trials and observational studies included in the MAH responses, are not sufficient to confirm any consistent statistically and clinically meaningful differences in inhibitor risk between the rFVIII and pdFVIII product classes.

In view of the above, the PRAC recommended the following updates of sections 4.4, 4.8 and 5.1 of the SmPC as well as sections 2 and 4 of the Package Leaflet for the FVIII products indicated for the

treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency) as follows:

- The section 4.4 of the SmPC should be amended to include a warning on the clinical importance of monitoring patients for FVIII inhibitor development (in particular warning on the clinical consequences of low compared to high titre inhibitors).
- With regards to sections 4.8 and 5.1 of the SmPC, the PRAC noted that several FVIII products currently include reference to data from study results which do not allow for a definite conclusion on the inhibitor risk for individual products. As the evidence suggests that all human FVIII products carry a risk of inhibitor development such statements should be removed. The available data supports a frequency of FVIII inhibitor development within the frequency of 'very common' and 'uncommon', for PUPs and PTPs respectively, therefore the PRAC recommends that the SmPCs should be aligned with these frequencies unless justified by product specific data. For products for which section 4.2 contains the following statement for PUPs: *"<Previously untreated patients. The safety and efficacy of {(Invented) name} in previously untreated patients have not yet been established. No data are available. >*), the above frequency for PUPs should not be implemented. In relation to section 5.1, any reference to inhibitor development studies in PUPs and PTPs should be deleted unless the studies were conducted in compliance with a Paediatric Investigation Plan or the studies provide robust evidence of a frequency of inhibitors in PUP which is less than *'very common'* or for PTPs which is different from *'uncommon'* (as laid down in the attachments of the PRAC AR).

Further to the assessment of the totality of the responses submitted by the MAH for susoctocog alfa (Obizur), the PRAC is of the opinion that the outcome of this article 31 referral procedure does not apply to this product in view of the indication of Obizur (acquired haemophilia A due to inhibitory antibodies to endogenous FVIII) and the different target population.

Benefit –risk balance

Based on the current evidence from the SIPPET study, as well as data from the individual clinical trials and observational studies included in the MAH responses, and the views expressed by the experts of the *ad-hoc* expert meeting, the PRAC agreed that the current evidence does not provide clear and consistent evidence of any statistically and clinically meaningful differences in inhibitor risk between rFVIII and pdFVIII products. No conclusions can be drawn on any role of VWF in protecting against inhibitor development.

Given these are heterogenous products, this does not preclude individual products being associated with an increased risk of inhibitor development in ongoing or future PUP studies.

Individual studies have identified a wide range of inhibitor frequency in PUPs across products, and the SIPPET study was not designed to differentiate between individual products in each class. Due to very different study methods and patient populations that have been studied over time, and inconsistent findings across studies, the PRAC found that the totality of evidence does not support a conclusion that recombinant factor VIII medicines, as a class, poses a greater risk of inhibitor development than the class derived from plasma.

Besides, the PRAC noted that several FVIII products currently include in their product information reference to data from study results which do not allow a definite conclusion on the inhibitor risk for individual products. As the evidence suggests that all human FVIII products carry a risk of inhibitor development, within the frequency of 'very common' and 'uncommon' for PUPs and PTPs respectively, the PRAC recommends that the SmPCs should be aligned with these frequencies unless justified by product specific data.

In view of the above, the PRAC concluded that the benefit-risk balance of Factor VIII products indicated for the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency), remains favourable subject to the changes to the product information agreed (section 4.4, 4.8 and 5.1 of the SmPC).

Re-examination procedure

Following the adoption of the PRAC recommendation during the May 2017 PRAC meeting, the MAH LFB Biomedicaments expressed their disagreement with the initial PRAC recommendation.

Given the detailed grounds provided by the MAH, the PRAC carried out a new assessment of the available data in the context of the re-examination.

PRAC discussion on grounds for re-examination

The SIPPET study was not designed to evaluate the risk of inhibitor development for individual products, and included a limited number of FVIII products. Due to heterogeneity across products, there is considerable uncertainty in extrapolating the findings of studies that have evaluated only class effects to individual products; and particularly to products (including more recently authorised products) which are not included in such studies. The findings from the SIPPET study, as well as those from the individual clinical trials and observational studies, are not sufficient to confirm any consistent statistically and clinically meaningful differences in inhibitor risk between the rFVIII and pdFVIII product classes.

Overall, the PRAC maintains its conclusions that standardised information on the frequency for FVIII products in PUP and PTP should be reflected in section 4.8 of the SmPC, unless another frequency range for a specific medicinal product is demonstrated by robust clinical studies for which the results would be summarised in section 5.1.

Expert consultation

The PRAC consulted an ad-hoc expert meeting on some of the aspects that formed part of the detailed grounds submitted by LFB Biomedicaments.

Overall, the expert group supported the PRAC initial conclusions and agreed that the proposed product information provides an adequate level of information to appropriately communicate to prescribers and patients about the risk of inhibitor development. No additional communication, on risk factors for inhibitor development beyond the product information or any additional risk minimisation measures was recommended.

The group also agreed that specific data about frequency of inhibitors for each product should not be included in the SmPC as the available studies are not adequately powered to draw precise conclusions on the absolute frequency for each product or on the relative frequency of inhibitors between products.

The experts emphasized that collaboration between academia, industry and regulators should be encouraged to collect harmonised data through registries.

PRAC conclusions

In conclusion, further to the initial assessment and the re-examination procedure, PRAC maintains its conclusion that the benefit-risk balance of the human plasma derived and recombinant coagulation Factor VIII containing medicinal products remains favourable subject to the agreed changes to the product information (section 4.4, 4.8 and 5.1 of the SmPC).

The PRAC adopted a recommendation on 01 September 2017 which was then considered by the CHMP, in accordance with Article 107k of Directive 2001/83/EC.

Overall summary of the scientific evaluation by the PRAC

Whereas,

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, for human plasma derived and recombinant coagulation factor VIII containing medicinal products (see Annex I and Annex A).
- The PRAC considered the totality of the data submitted with regards to the risk of inhibitor development for the classes of recombinant and plasma derived FVIII products, in previously untreated patients (PUPs). This included published literature (SIPPET study[6]), data generated in individual clinical trials and a range of observational studies submitted by the marketing authorisation holders, including the data generated in large multicentre cohort studies, data submitted by the national competent authorities of the EU Member States as well as responses provided by the Authors of the SIPPET study. PRAC also considered grounds submitted by LFB Biomedicaments as basis for their request for re-examination of the PRAC recommendation and the views of two experts meetings held on 22 February and 3 August 2017.
- The PRAC noted that the SIPPET study was not designed to evaluate the risk of inhibitor development for individual products, and included a limited number of FVIII products in total. Due to the heterogeneity across products, there is considerable uncertainty in extrapolating the findings of studies evaluating only class effects to individual products; and particularly to the products that are not included in such studies.
- The PRAC also considered that studies conducted to date suffer from a variety of methodological limitations and, on balance, there is no clear and consistent evidence to suggest differences in relative risks between FVIII product classes based on available data. Specifically, the findings from the SIPPET study, as well as those from the individual clinical trials and observational studies included in the MAH responses, are not sufficient to confirm any consistent statistically and clinically meaningful differences in inhibitor risk between rFVIII and pdFVIII product classes. Given these are heterogenous products, this does not preclude individual products being associated with an increased risk of inhibitor development in ongoing or future PUP studies.
- The PRAC noted that the efficacy and safety of Factor VIII products as indicated in the treatment and prophylaxis of bleeding in patients with haemophilia A have been established.Based on the available data, the PRAC considered that SmPC updates for the FVIII products are warranted: section 4.4 should be amended to include a warning on the clinical importance of monitoring patients for FVIII inhibitor development. With regards to sections 4.8 and 5.1, the PRAC noted that several FVIII products currently include reference to data from study results which do not allow a definite conclusion on the inhibitor risk for individual products. Results of clinical studies not sufficiently robust (e.g. suffering from methodolical limitations) should not be reflected in the product information on FVIIII products. The PRAC recommended changes to the product information accordingly. Besides, as the evidence suggests that all human FVIII products carry a risk of inhibitor development, within the frequency of 'very common' and 'uncommon', for PUPs and PTPs respectively, the PRAC recommended that the product information of these products should be aligned with these frequencies unless justified by product specific data.

Therefore, the PRAC concluded that the benefit-risk balance of the human plasma derived and recombinant coagulation Factor VIII containing medicinal products remains favourable and recommended the variations to the terms of the marketing authorisations.

[6] Peyvandi F, Mannucci PM, Garagiola I, et al. A Randomized Trial of Factor VIII and Neutralizing Antibodies in Hemophilia A. The New England journal of medicine 2016 May 26;374(21):2054-64

CHMP opinion

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.