ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer 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. KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer. 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.

KOGENATE Bayer 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
KOGENATE Bayer 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 KOGENATE Bayer. 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 KOGENATE Bayer 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 KOGENATE Bayer with other medicinal products have been reported.

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with KOGENATE Bayer.

Pregnancy and breast-feeding
Based on the rare occurrence of haemophilia A in women, experience regarding the use of KOGENATE Bayer during pregnancy and breast-feeding is not available. Therefore, KOGENATE Bayer 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

KOGENATE Bayer 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, KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer (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 KOGENATE Bayer, 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 KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer has been used to induce immune tolerance. In patients where immune tolerance was achieved the bleedings could be prevented or controlled with KOGENATE Bayer 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 KOGENATE Bayer. This result is similar to the reported values for factor VIII derived from human plasma.

Distribution and elimination
After administration of KOGENATE Bayer, 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 KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer, since no mutagenic potential could be detected *in vitro* or *in vivo* for the predecessor product of KOGENATE Bayer.

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 components (powder vial with Bio-Set device, pre-filled syringe containing solvent and venipuncture set) should be used for reconstitution and injection 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 vial and the pre-filled syringe 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 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 KOGENATE Bayer contains:
- one vial plus Bio-Set device, containing powder (10 ml clear glass type 1 vial with latex-free grey halogenobutyl rubber blend stopper plus transfer device with protective cap [Bio-Set])
- one pre-filled syringe with 2.5 ml solvent (clear glass cylinder type 1 with latex-free grey bromobutyl rubber blend stopper)
- syringe plunger rod
- one venipuncture set
- two alcohol swabs for single use
- two dry swabs
- two plasters

6.6 Special precautions for disposal and other handling

Detailed instructions for preparation and administration are contained in the package leaflet provided with KOGENATE Bayer.

KOGENATE Bayer powder should only be reconstituted with the supplied solvent (2.5 ml water for injections) in the prefilled syringe and the integrated transfer device (Bio-Set). 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 KOGENATE Bayer if you notice visible particulate matter or turbidity.

After reconstitution, the solution is drawn back into the syringe. KOGENATE Bayer 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 can be achieved by following the reconstitution and/or administration steps as described in the package leaflet provided with KOGENATE Bayer. It is important to use the venipuncture set provided with the product for administration as it incorporates an in-line filter.
In situations where the venipuncture set provided cannot be used (e.g. when infusing into a peripheral or central line), a separate filter compatible with KOGENATE Bayer should be used. These compatible filters are luer adaptor-type of Polyacrylic housing with integrated filter element of a Polyamide screen of 5 – 20 micrometer mesh size.

The venipuncture set provided with the product must not be used for drawing blood because it contains an in-line filter. When blood must be withdrawn prior to an infusion, use an administration set without a filter, then infuse KOGENATE Bayer through an injection filter.
If you have any questions about KOGENATE Bayer and compatible separate filters contact Bayer Pharma AG.

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/1/00/143/004

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

KOGENATE Bayer 500 IU powder and solvent for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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Human coagulation factor VIII is produced by recombinant DNA technology (rDNA) in baby hamster kidney cells containing the human factor VIII gene.

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One ml of KOGENATE Bayer 500 IU contains approximately 200 IU (500 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 KOGENATE Bayer is approximately 4000 IU/mg protein.

Solvent: water for injections.

For the full list of excipients, see section 6.1.

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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

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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).

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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.

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.

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Intravenous use.

KOGENATE Bayer 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).

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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
	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 KOGENATE Bayer. 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 KOGENATE Bayer 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 KOGENATE Bayer with other medicinal products have been reported.

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with KOGENATE Bayer.

Pregnancy and breast-feeding
Based on the rare occurrence of haemophilia A in women, experience regarding the use of KOGENATE Bayer during pregnancy and breast-feeding is not available. Therefore, KOGENATE Bayer 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

KOGENATE Bayer 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, KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer (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 KOGENATE Bayer, 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 KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer has been used to induce immune tolerance. In patients where immune tolerance was achieved the bleedings could be prevented or controlled with KOGENATE Bayer 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 KOGENATE Bayer. This result is similar to the reported values for factor VIII derived from human plasma.

Distribution and elimination
After administration of KOGENATE Bayer, 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 KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer, since no mutagenic potential could be detected *in vitro* or *in vivo* for the predecessor product of KOGENATE Bayer.

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 components (powder vial with Bio-Set device, pre-filled syringe containing solvent and venipuncture set) should be used for reconstitution and injection 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 vial and the pre-filled syringe 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 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 KOGENATE Bayer contains:
- one vial plus Bio-Set device, containing powder (10 ml clear glass type 1 vial with latex-free grey halogenobutyl rubber blend stopper plus transfer device with protective cap [Bio-Set])
- one pre-filled syringe with 2.5 ml solvent (clear glass cylinder type 1 with latex-free grey bromobutyl rubber blend stopper)
- syringe plunger rod
- one venipuncture set
- two alcohol swabs for single use
- two dry swabs
- two plasters

6.6 Special precautions for disposal and other handling

Detailed instructions for preparation and administration are contained in the package leaflet provided with KOGENATE Bayer.

KOGENATE Bayer powder should only be reconstituted with the supplied solvent (2.5 ml water for injections) in the prefilled syringe and the integrated transfer device (Bio-Set). 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 KOGENATE Bayer if you notice visible particulate matter or turbidity.

After reconstitution, the solution is drawn back into the syringe. KOGENATE Bayer 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 can be achieved by following the reconstitution and/or administration steps as described in the package leaflet provided with KOGENATE Bayer. It is important to use the venipuncture set provided with the product for administration as it incorporates an in-line filter.
In situations where the venipuncture set provided cannot be used (e.g. when infusing into a peripheral or central line), a separate filter compatible with KOGENATE Bayer should be used. These compatible filters are luer adaptor-type of Polyacrylic housing with integrated filter element of a Polyamide screen of 5 – 20 micrometer mesh size.

The venipuncture set provided with the product must not be used for drawing blood because it contains an in-line filter. When blood must be withdrawn prior to an infusion, use an administration set without a filter, then infuse KOGENATE Bayer through an injection filter.
If you have any questions about KOGENATE Bayer and compatible separate filters contact Bayer Pharma AG.

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/1/00/143/005

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.

1. NAME OF THE MEDICINAL PRODUCT

KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer 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. KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer. 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.

KOGENATE Bayer 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
KOGENATE Bayer 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 KOGENATE Bayer. 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 KOGENATE Bayer 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 KOGENATE Bayer with other medicinal products have been reported.

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with KOGENATE Bayer.

Pregnancy and breast-feeding
Based on the rare occurrence of haemophilia A in women, experience regarding the use of KOGENATE Bayer during pregnancy and breast-feeding is not available. Therefore, KOGENATE Bayer 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

KOGENATE Bayer 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, KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer (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 KOGENATE Bayer, 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 KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer has been used to induce immune tolerance. In patients where immune tolerance was achieved the bleedings could be prevented or controlled with KOGENATE Bayer 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 KOGENATE Bayer. This result is similar to the reported values for factor VIII derived from human plasma.

Distribution and elimination
After administration of KOGENATE Bayer, 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 KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer, since no mutagenic potential could be detected *in vitro* or *in vivo* for the predecessor product of KOGENATE Bayer.

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 components (powder vial with Bio-Set device, pre-filled syringe containing solvent and venipuncture set) should be used for reconstitution and injection 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 vial and the pre-filled syringe 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 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 KOGENATE Bayer contains:
- one vial plus Bio-Set device, containing powder (10 ml clear glass type 1 vial with latex-free grey halogenobutyl rubber blend stopper plus transfer device with protective cap [Bio-Set])
- one pre-filled syringe with 2.5 ml solvent (clear glass cylinder type 1 with latex-free grey bromobutyl rubber blend stopper)
- syringe plunger rod
- one venipuncture set
- two alcohol swabs for single use
- two dry swabs
- two plasters

6.6 Special precautions for disposal and other handling

Detailed instructions for preparation and administration are contained in the package leaflet provided with KOGENATE Bayer.

KOGENATE Bayer powder should only be reconstituted with the supplied solvent (2.5 ml water for injections) in the prefilled syringe and the integrated transfer device (Bio-Set). 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 KOGENATE Bayer if you notice visible particulate matter or turbidity.

After reconstitution, the solution is drawn back into the syringe. KOGENATE Bayer 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 can be achieved by following the reconstitution and/or administration steps as described in the package leaflet provided with KOGENATE Bayer. It is important to use the venipuncture set provided with the product for administration as it incorporates an in-line filter.
In situations where the venipuncture set provided cannot be used (e.g. when infusing into a peripheral or central line), a separate filter compatible with KOGENATE Bayer should be used. These compatible filters are luer adaptor-type of Polyacrylic housing with integrated filter element of a Polyamide screen of 5 – 20 micrometer mesh size.

The venipuncture set provided with the product must not be used for drawing blood because it contains an in-line filter. When blood must be withdrawn prior to an infusion, use an administration set without a filter, then infuse KOGENATE Bayer through an injection filter.
If you have any questions about KOGENATE Bayer and compatible separate filters contact Bayer Pharma AG.

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/1/00/143/006

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

KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer 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. KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer. 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.

KOGENATE Bayer 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
KOGENATE Bayer 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 KOGENATE Bayer. 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 KOGENATE Bayer 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 KOGENATE Bayer with other medicinal products have been reported.

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with KOGENATE Bayer.

Pregnancy and breast-feeding
Based on the rare occurrence of haemophilia A in women, experience regarding the use of KOGENATE Bayer during pregnancy and breast-feeding is not available. Therefore, KOGENATE Bayer 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

KOGENATE Bayer 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, KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer (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 KOGENATE Bayer, 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.

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Continuous Infusion
It has been shown in a clinical study performed with adult haemophilia A patients who undergo a major surgery that KOGENATE Bayer 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
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Immune Tolerance Induction (ITI)
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Absorption
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No studies were performed on the mutagenic potential of KOGENATE Bayer, since no mutagenic potential could be detected *in vitro* or *in vivo* for the predecessor product of KOGENATE Bayer.

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 components (powder vial with Bio-Set device, pre-filled syringe containing solvent and venipuncture set) should be used for reconstitution and injection 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 vial and the pre-filled syringe 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 outer carton.

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Each package of KOGENATE Bayer contains:
- one vial plus Bio-Set device, containing powder (10 ml clear glass type 1 vial with latex-free grey halogenobutyl rubber blend stopper plus transfer device with protective cap [Bio-Set])
- one pre-filled syringe with 5.0 ml solvent (clear glass cylinder type 1 with latex-free grey bromobutyl rubber blend stopper)
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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 KOGENATE Bayer if you notice visible particulate matter or turbidity.

After reconstitution, the solution is drawn back into the syringe. KOGENATE Bayer 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 can be achieved by following the reconstitution and/or administration steps as described in the package leaflet provided with KOGENATE Bayer. It is important to use the venipuncture set provided with the product for administration as it incorporates an in-line filter.
In situations where the venipuncture set provided cannot be used (e.g. when infusing into a peripheral or central line), a separate filter compatible with KOGENATE Bayer should be used. These compatible filters are luer adaptor-type of Polyacrylic housing with integrated filter element of a Polyamide screen of 5 – 20 micrometer mesh size.

The venipuncture set provided with the product must not be used for drawing blood because it contains an in-line filter. When blood must be withdrawn prior to an infusion, use an administration set without a filter, then infuse KOGENATE Bayer through an injection filter.
If you have any questions about KOGENATE Bayer and compatible separate filters contact Bayer Pharma AG.

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/1/00/143/010

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

KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer 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. KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer. 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.

KOGENATE Bayer 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
KOGENATE Bayer 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 KOGENATE Bayer. 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 KOGENATE Bayer 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 KOGENATE Bayer with other medicinal products have been reported.

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with KOGENATE Bayer.

Pregnancy and breast-feeding
Based on the rare occurrence of haemophilia A in women, experience regarding the use of KOGENATE Bayer during pregnancy and breast-feeding is not available. Therefore, KOGENATE Bayer 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

KOGENATE Bayer 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, KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer (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 KOGENATE Bayer, 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 KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer has been used to induce immune tolerance. In patients where immune tolerance was achieved the bleedings could be prevented or controlled with KOGENATE Bayer 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 KOGENATE Bayer. This result is similar to the reported values for factor VIII derived from human plasma.

Distribution and elimination
After administration of KOGENATE Bayer, 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 KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer, since no mutagenic potential could be detected *in vitro* or *in vivo* for the predecessor product of KOGENATE Bayer.

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 components (powder vial with Bio-Set device, pre-filled syringe containing solvent and venipuncture set) should be used for reconstitution and injection 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 vial and the pre-filled syringe 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 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 KOGENATE Bayer contains:
- one vial plus Bio-Set device, containing powder (10 ml clear glass type 1 vial with latex-free grey halogenobutyl rubber blend stopper plus transfer device with protective cap [Bio-Set])
- one pre-filled syringe with 5.0 ml solvent (clear glass cylinder type 1 with latex-free grey bromobutyl rubber blend stopper)
- syringe plunger rod
- one venipuncture set
- two alcohol swabs for single use
- two dry swabs
- two plasters

6.6 Special precautions for disposal and other handling

Detailed instructions for preparation and administration are contained in the package leaflet provided with KOGENATE Bayer.

KOGENATE Bayer powder should only be reconstituted with the supplied solvent (5.0 ml water for injections) in the prefilled syringe and the integrated transfer device (Bio-Set). 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 KOGENATE Bayer if you notice visible particulate matter or turbidity.

After reconstitution, the solution is drawn back into the syringe. KOGENATE Bayer 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 can be achieved by following the reconstitution and/or administration steps as described in the package leaflet provided with KOGENATE Bayer. It is important to use the venipuncture set provided with the product for administration as it incorporates an in-line filter.
In situations where the venipuncture set provided cannot be used (e.g. when infusing into a peripheral or central line), a separate filter compatible with KOGENATE Bayer should be used. These compatible filters are luer adaptor-type of Polyacrylic housing with integrated filter element of a Polyamide screen of 5 – 20 micrometer mesh size.

The venipuncture set provided with the product must not be used for drawing blood because it contains an in-line filter. When blood must be withdrawn prior to an infusion, use an administration set without a filter, then infuse KOGENATE Bayer through an injection filter.
If you have any questions about KOGENATE Bayer and compatible separate filters contact Bayer Pharma AG.

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/1/00/143/012

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

KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer 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. KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer. 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.

KOGENATE Bayer 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
KOGENATE Bayer 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 KOGENATE Bayer. 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 KOGENATE Bayer 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 KOGENATE Bayer with other medicinal products have been reported.

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with KOGENATE Bayer.

Pregnancy and breast-feeding
Based on the rare occurrence of haemophilia A in women, experience regarding the use of KOGENATE Bayer during pregnancy and breast-feeding is not available. Therefore, KOGENATE Bayer 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

KOGENATE Bayer 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, KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer (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 KOGENATE Bayer, 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 KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer has been used to induce immune tolerance. In patients where immune tolerance was achieved the bleedings could be prevented or controlled with KOGENATE Bayer 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 KOGENATE Bayer. This result is similar to the reported values for factor VIII derived from human plasma.

Distribution and elimination
After administration of KOGENATE Bayer, 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 KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer, since no mutagenic potential could be detected *in vitro* or *in vivo* for the predecessor product of KOGENATE Bayer.

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 components (powder vial, pre-filled syringe containing solvent, vial adapter and venipuncture set) should be used for reconstitution and injection 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 vial and the pre-filled syringe 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 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 KOGENATE Bayer contains:
- one vial with powder (10 ml clear glass type 1 vial with latex-free grey halogenobutyl rubber blend stopper and aluminium seal)
- one pre-filled syringe with 2.5 ml solvent (clear glass cylinder type 1 with latex-free grey bromobutyl rubber blend stopper)
- syringe plunger rod
- vial adapter
- one venipuncture set
- two alcohol swabs for single use
- two dry swabs
- two plasters

6.6 Special precautions for disposal and other handling

Detailed instructions for preparation and administration are contained in the package leaflet provided with KOGENATE Bayer.

KOGENATE Bayer powder should only be reconstituted with the supplied solvent (2.5 ml water for injections) in the prefilled syringe and the vial adapter. 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 KOGENATE Bayer if you notice visible particulate matter or turbidity.

After reconstitution, the solution is drawn back into the syringe. KOGENATE Bayer 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 vial 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/1/00/143/007

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

KOGENATE Bayer 500 IU powder and solvent for solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2.1 General description

Each vial contains nominally 500 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 KOGENATE Bayer 500 IU contains approximately 200 IU (500 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 KOGENATE Bayer 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. KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer. 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.

KOGENATE Bayer 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
KOGENATE Bayer 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 KOGENATE Bayer. 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 KOGENATE Bayer 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 KOGENATE Bayer with other medicinal products have been reported.

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with KOGENATE Bayer.

Pregnancy and breast-feeding
Based on the rare occurrence of haemophilia A in women, experience regarding the use of KOGENATE Bayer during pregnancy and breast-feeding is not available. Therefore, KOGENATE Bayer 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

KOGENATE Bayer 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, KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer (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 KOGENATE Bayer, 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 KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer has been used to induce immune tolerance. In patients where immune tolerance was achieved the bleedings could be prevented or controlled with KOGENATE Bayer 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 KOGENATE Bayer. This result is similar to the reported values for factor VIII derived from human plasma.

Distribution and elimination
After administration of KOGENATE Bayer, 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 KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer, since no mutagenic potential could be detected *in vitro* or *in vivo* for the predecessor product of KOGENATE Bayer.

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 components (powder vial, pre-filled syringe containing solvent, vial adapter and venipuncture set) should be used for reconstitution and injection 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 vial and the pre-filled syringe 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 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 KOGENATE Bayer contains:
- one vial with powder (10 ml clear glass type 1 vial with latex-free grey halogenobutyl rubber blend stopper and aluminium seal)
- one pre-filled syringe with 2.5 ml solvent (clear glass cylinder type 1 with latex-free grey bromobutyl rubber blend stopper)
- syringe plunger rod
- vial adapter
- one venipuncture set
- two alcohol swabs for single use
- two dry swabs
- two plasters

6.6 Special precautions for disposal and other handling

Detailed instructions for preparation and administration are contained in the package leaflet provided with KOGENATE Bayer.

KOGENATE Bayer powder should only be reconstituted with the supplied solvent (2.5 ml water for injections) in the prefilled syringe and the vial adapter. 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 KOGENATE Bayer if you notice visible particulate matter or turbidity.

After reconstitution, the solution is drawn back into the syringe. KOGENATE Bayer 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 vial 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/1/00/143/008

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

KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer 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. KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer. 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.

KOGENATE Bayer 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
KOGENATE Bayer 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 KOGENATE Bayer. 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 KOGENATE Bayer 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 KOGENATE Bayer with other medicinal products have been reported.

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with KOGENATE Bayer.

Pregnancy and breast-feeding
Based on the rare occurrence of haemophilia A in women, experience regarding the use of KOGENATE Bayer during pregnancy and breast-feeding is not available. Therefore, KOGENATE Bayer 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

KOGENATE Bayer 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, KOGENATE Bayer 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 KOGENATE Bayer developed inhibitors within 20 exposure days.

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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.

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Immune Tolerance Induction (ITI)
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6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.
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6.3 Shelf-life

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Do not refrigerate after reconstitution.

6.4 Special precautions for storage

Store in a refrigerator (2°C – 8°C). Do not freeze. Keep the vial and the pre-filled syringe in the outer carton in order to protect from light.

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- one pre-filled syringe with 2.5 ml solvent (clear glass cylinder type 1 with latex-free grey bromobutyl rubber blend stopper)
- syringe plunger rod
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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 KOGENATE Bayer if you notice visible particulate matter or turbidity.

After reconstitution, the solution is drawn back into the syringe. KOGENATE Bayer 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 vial 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/1/00/143/009

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

KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer 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. KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer. 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.

KOGENATE Bayer 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
KOGENATE Bayer 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 KOGENATE Bayer. 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 KOGENATE Bayer 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 KOGENATE Bayer with other medicinal products have been reported.

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with KOGENATE Bayer.

Pregnancy and breast-feeding
Based on the rare occurrence of haemophilia A in women, experience regarding the use of KOGENATE Bayer during pregnancy and breast-feeding is not available. Therefore, KOGENATE Bayer 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

KOGENATE Bayer 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, KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer (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 KOGENATE Bayer, 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 KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer has been used to induce immune tolerance. In patients where immune tolerance was achieved the bleedings could be prevented or controlled with KOGENATE Bayer 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 KOGENATE Bayer. This result is similar to the reported values for factor VIII derived from human plasma.

Distribution and elimination
After administration of KOGENATE Bayer, 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 KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer, since no mutagenic potential could be detected *in vitro* or *in vivo* for the predecessor product of KOGENATE Bayer.

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 components (powder vial, pre-filled syringe containing solvent, vial adapter and venipuncture set) should be used for reconstitution and injection 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 vial and the pre-filled syringe 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 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 KOGENATE Bayer contains:
- one vial with powder (10 ml clear glass type 1 vial with latex-free grey halogenobutyl rubber blend stopper and aluminium seal)
- one pre-filled syringe with 5.0 ml solvent (clear glass cylinder type 1 with latex-free grey bromobutyl rubber blend stopper)
- syringe plunger rod
- vial adapter
- one venipuncture set
- two alcohol swabs for single use
- two dry swabs
- two plasters

6.6 Special precautions for disposal and other handling

Detailed instructions for preparation and administration are contained in the package leaflet provided with KOGENATE Bayer.

KOGENATE Bayer powder should only be reconstituted with the supplied solvent (5.0 ml water for injections) in the prefilled syringe and the vial adapter. 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 KOGENATE Bayer if you notice visible particulate matter or turbidity.

After reconstitution, the solution is drawn back into the syringe. KOGENATE Bayer 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 vial 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/1/00/143/011

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

KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer 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. KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer. 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.

KOGENATE Bayer 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
KOGENATE Bayer 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 KOGENATE Bayer. 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 KOGENATE Bayer 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 KOGENATE Bayer with other medicinal products have been reported.

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with KOGENATE Bayer.

Pregnancy and breast-feeding
Based on the rare occurrence of haemophilia A in women, experience regarding the use of KOGENATE Bayer during pregnancy and breast-feeding is not available. Therefore, KOGENATE Bayer 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

KOGENATE Bayer 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, KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer (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 KOGENATE Bayer, 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 KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer has been used to induce immune tolerance. In patients where immune tolerance was achieved the bleedings could be prevented or controlled with KOGENATE Bayer 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 KOGENATE Bayer. This result is similar to the reported values for factor VIII derived from human plasma.

Distribution and elimination
After administration of KOGENATE Bayer, 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 KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer, since no mutagenic potential could be detected *in vitro* or *in vivo* for the predecessor product of KOGENATE Bayer.

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 components (powder vial, pre-filled syringe containing solvent, vial adapter and venipuncture set) should be used for reconstitution and injection 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 vial and the pre-filled syringe 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 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 KOGENATE Bayer contains:
- one vial with powder (10 ml clear glass type 1 vial with latex-free grey halogenobutyl rubber blend stopper and aluminium seal)
- one pre-filled syringe with 5.0 ml solvent (clear glass cylinder type 1 with latex-free grey bromobutyl rubber blend stopper)
- syringe plunger rod
- vial adapter
- one venipuncture set
- two alcohol swabs for single use
- two dry swabs
- two plasters

6.6 Special precautions for disposal and other handling

Detailed instructions for preparation and administration are contained in the package leaflet provided with KOGENATE Bayer.

KOGENATE Bayer powder should only be reconstituted with the supplied solvent (5.0 ml water for injections) in the prefilled syringe and the vial adapter. 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 KOGENATE Bayer if you notice visible particulate matter or turbidity.

After reconstitution, the solution is drawn back into the syringe. KOGENATE Bayer 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 vial 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/1/00/143/013

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

KOGENATE Bayer 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 Bio-Set device with powder for solution for injection.
1 pre-filled syringe with 2.5 ml water for injections with separate plunger rod.
1 venipuncture set
2 alcohol swabs for single use
2 dry swabs
2 plasters

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 vial and the pre-filled syringe 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/1/00/143/004

13. BATCH NUMBER

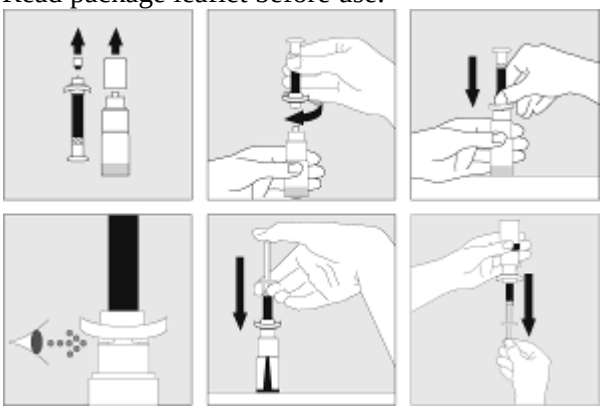
Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Read package leaflet before use.



16. INFORMATION IN BRAILLE

KOGENATE Bayer 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

KOGENATE Bayer 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

Bayer-Logo

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE 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

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

KOGENATE Bayer 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 Bio-Set device with powder for solution for injection.
1 pre-filled syringe with 2.5 ml water for injections with separate plunger rod.
1 venipuncture set
2 alcohol swabs for single use
2 dry swabs
2 plasters

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 vial and the pre-filled syringe 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/1/00/143/005

13. BATCH NUMBER

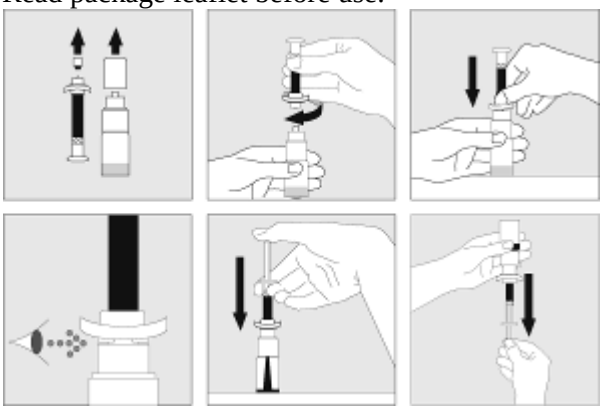
Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Read package leaflet before use.



16. INFORMATION IN BRAILLE

KOGENATE Bayer 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

KOGENATE Bayer 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

Bayer-Logo

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE 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

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

KOGENATE Bayer 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 Bio-Set device with powder for solution for injection.
1 pre-filled syringe with 2.5 ml water for injections with separate plunger rod.
1 venipuncture set
2 alcohol swabs for single use
2 dry swabs
2 plasters

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 vial and the pre-filled syringe 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/1/00/143/006

13. BATCH NUMBER

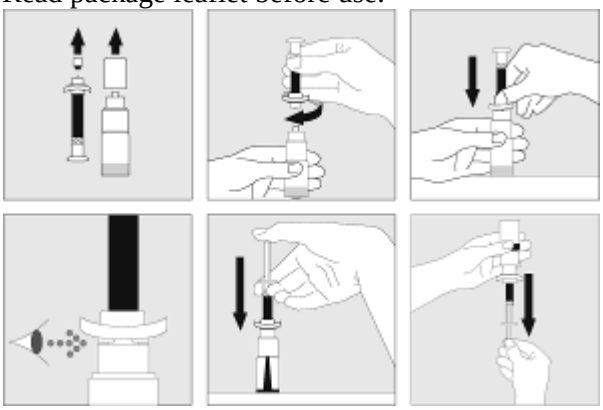
Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Read package leaflet before use.



16. INFORMATION IN BRAILLE

KOGENATE Bayer 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

KOGENATE Bayer 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

Bayer-Logo

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE 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

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

KOGENATE Bayer 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 Bio-Set device with powder for solution for injection.
1 pre-filled syringe with 5.0 ml water for injections with separate plunger rod.
1 venipuncture set
2 alcohol swabs for single use
2 dry swabs
2 plasters

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 vial and the pre-filled syringe 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/1/00/143/010

13. BATCH NUMBER

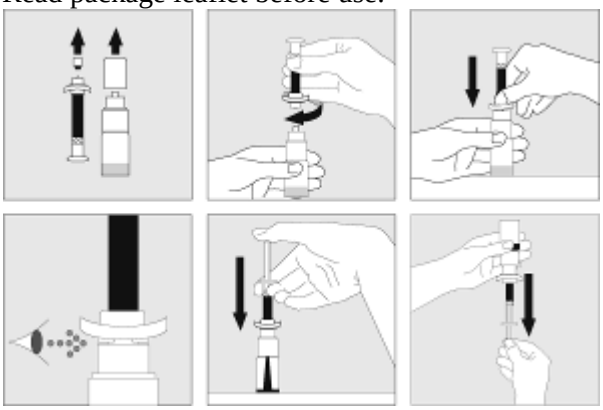
Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Read package leaflet before use.



16. INFORMATION IN BRAILLE

KOGENATE Bayer 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

KOGENATE Bayer 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

Bayer-Logo

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE 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

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

KOGENATE Bayer 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 Bio-Set device with powder for solution for injection.
1 pre-filled syringe with 5.0 ml water for injections with separate plunger rod.
1 venipuncture set
2 alcohol swabs for single use
2 dry swabs
2 plasters

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 vial and the pre-filled syringe 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/1/00/143/012

13. BATCH NUMBER

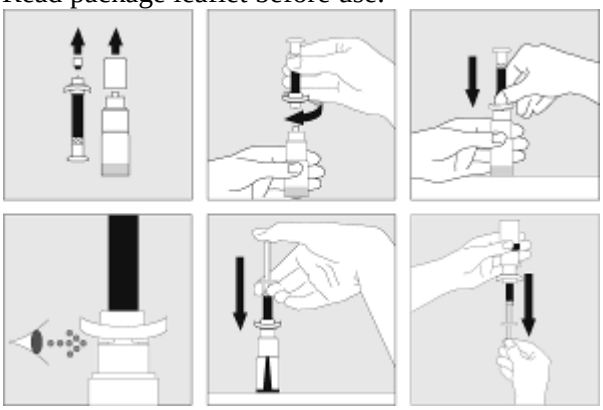
Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Read package leaflet before use.



16. INFORMATION IN BRAILLE

KOGENATE Bayer 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

KOGENATE Bayer 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

Bayer-Logo

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE 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

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

KOGENATE Bayer 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 pre-filled syringe with 2.5 ml water for injections with separate plunger rod.
1 vial adapter
1 venipuncture set
2 alcohol swabs for single use
2 dry swabs
2 plasters

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 vial and the pre-filled syringe 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/1/00/143/007

13. BATCH NUMBER

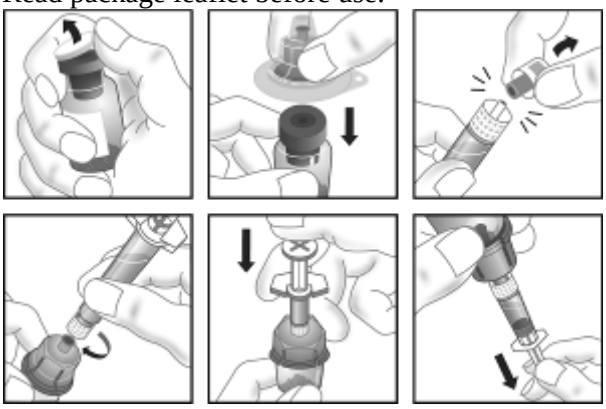
Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Read package leaflet before use.



16. INFORMATION IN BRAILLE

KOGENATE Bayer 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

KOGENATE Bayer 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

Bayer-Logo

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE 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

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

KOGENATE Bayer 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 pre-filled syringe with 2.5 ml water for injections with separate plunger rod.
1 vial adapter
1 venipuncture set
2 alcohol swabs for single use
2 dry swabs
2 plasters

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 vial and the pre-filled syringe 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/1/00/143/008

13. BATCH NUMBER

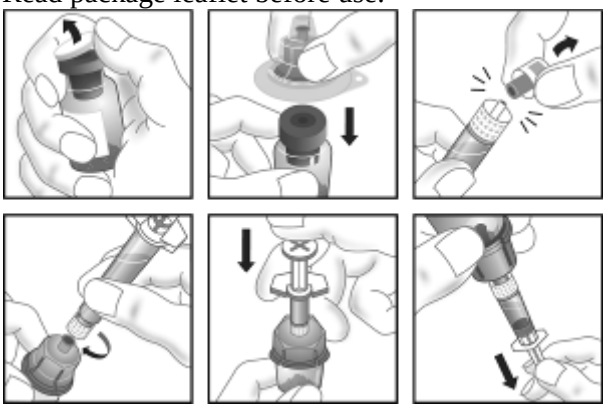
Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Read package leaflet before use.



16. INFORMATION IN BRAILLE

KOGENATE Bayer 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

KOGENATE Bayer 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

Bayer-Logo

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE 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

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

KOGENATE Bayer 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 pre-filled syringe with 2.5 ml water for injections with separate plunger rod.
1 vial adapter
1 venipuncture set
2 alcohol swabs for single use
2 dry swabs
2 plasters

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 vial and the pre-filled syringe 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/1/00/143/009

13. BATCH NUMBER

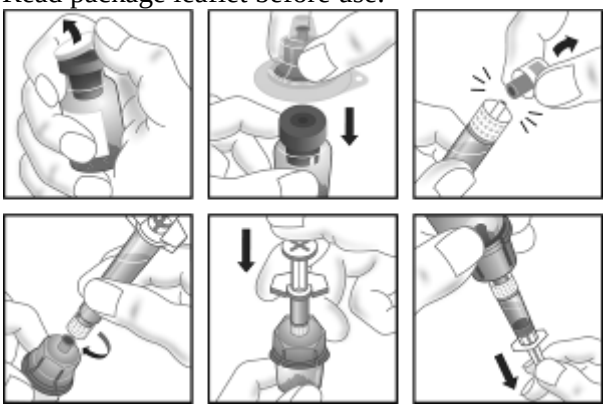
Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Read package leaflet before use.



16. INFORMATION IN BRAILLE

KOGENATE Bayer 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

KOGENATE Bayer 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

Bayer-Logo

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE 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

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

KOGENATE Bayer 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 pre-filled syringe with 5.0 ml water for injections with separate plunger rod.
1 vial adapter
1 venipuncture set
2 alcohol swabs for single use
2 dry swabs
2 plasters

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 vial and the pre-filled syringe 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/1/00/143/011

13. BATCH NUMBER

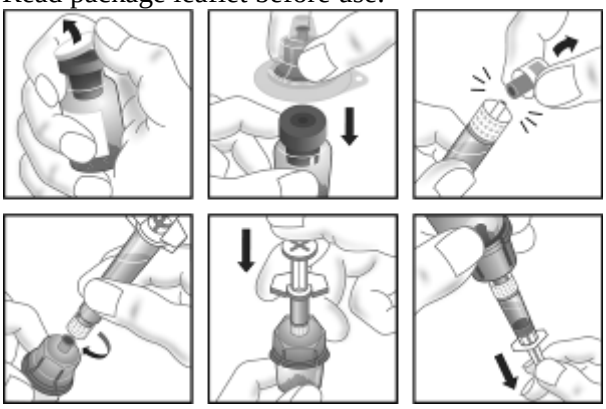
Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Read package leaflet before use.



16. INFORMATION IN BRAILLE

KOGENATE Bayer 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

KOGENATE Bayer 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

Bayer-Logo

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE 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

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

KOGENATE Bayer 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 pre-filled syringe with 5.0 ml water for injections with separate plunger rod.
1 vial adapter
1 venipuncture set
2 alcohol swabs for single use
2 dry swabs
2 plasters

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 vial and the pre-filled syringe 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/1/00/143/013

13. BATCH NUMBER

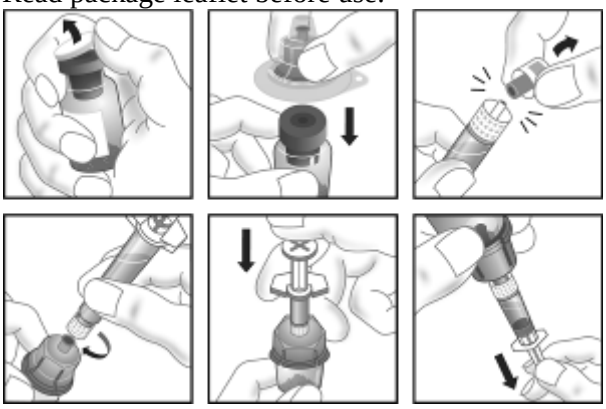
Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

Read package leaflet before use.



16. INFORMATION IN BRAILLE

KOGENATE Bayer 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

KOGENATE Bayer 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

Bayer-Logo

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

PRE-FILLED SYRINGE 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

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

KOGENATE Bayer 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 KOGENATE Bayer 250 IU is and what it is used for

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

KOGENATE Bayer is used for treatment and prophylaxis of bleeding in 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.

Each pack of KOGENATE Bayer 250 IU contains a vial with Bio-Set transfer device and a pre-filled syringe with a separate plunger rod, as well as a venipuncture set (for injection into a vein), two alcohol swabs, two dry swabs and two plasters.
The vial contains a dry white to slightly yellow powder or cake. The pre-filled syringe contains 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 KOGENATE Bayer 250 IU

Do not use KOGENATE Bayer 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 KOGENATE Bayer 250 IU.

Take special care with KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer 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.

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

3. How to use KOGENATE Bayer 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 (powder vial with Bio-Set device, pre-filled syringe containing solvent and venipuncture set) for reconstitution and administration that are

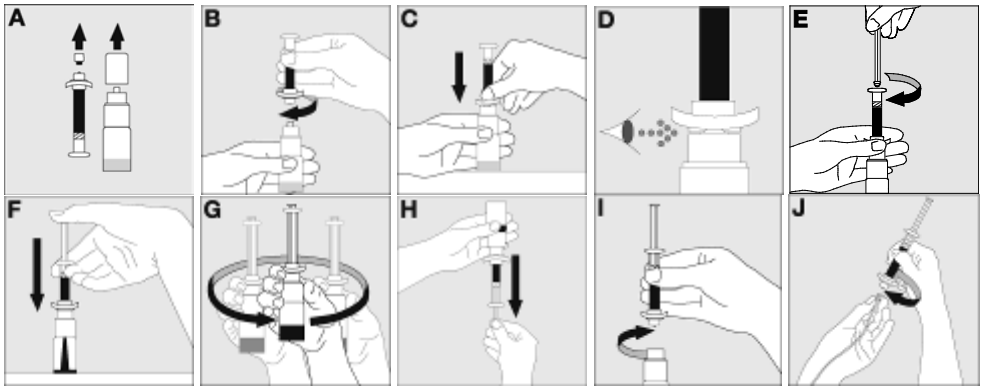
provided with each package of this medicine. If these components cannot be used, please contact your doctor. If any component of the package is opened or damaged, do not use it

- You must filter the reconstituted product before administration to remove potential particulate matter in the solution. Filtering can be achieved by following the reconstitution and/or administration steps as described below. Use the venipuncture set provided as it contains an in-line filter. If you cannot use the venipuncture set provided, use a separate filter which is compatible with KOGENATE Bayer. These compatible filters are luer adaptor-type of Polyacrylic housing with integrated filter element of a Polyamide screen of 5 – 20 micrometer mesh size.

- Do not use the venipuncture set provided for drawing blood because it contains an in-line filter. When you must withdraw blood before an infusion, use an administration set without a filter, then infuse KOGENATE Bayer through an injection filter. If you have any questions about KOGENATE Bayer and compatible separate filters contact your doctor.

- This medicine must **not** be mixed with other infusion solutions. 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. The solution must be prepared on a clean and dry surface.
2. Warm the unopened powder vial and the solvent syringe in your hands until they feel as warm as your hands. The material should not be warmer than body temperature (not exceed 37 °C). Wipe any observable moisture from the vial.
3. Remove the cap from the powder vial by gently moving it from side to side several times, whilst at the same time pulling upwards. Remove the stopper attached to the white cap from the syringe (**A**).
4. Gently screw the syringe on to the powder vial (**B**).
5. Place the vial on a rigid, non-slip surface and hold it firmly with one hand. Then, strongly press down the fingerplate near the syringe tip using your thumb and index finger (**C**) until the finger plate meets the top edge of the Bio-Set. This indicates that the system is activated (**D**).
6. Connect the plunger rod to the syringe by screwing it into the rubber stopper (**E**).
7. Inject the solvent into the vial containing the powder by slowly pushing the syringe plunger down (**F**).
8. Dissolve the powder by gently swirling the vial. Do not shake the vial! Ensure that the powder is completely dissolved before use. Inspect visually for particulate matter and discoloration prior to administration. Do not use solutions that contain visible particles or that are cloudy (**G**).
9. Invert vial/syringe and transfer the solution into syringe by drawing the plunger out slowly and smoothly (**H**). Ensure that the entire contents of the vial are drawn into the syringe.

10. Apply a tourniquet. Determine the point of injection, clean the skin with an alcohol swab, and prepare site of injection antiseptically as advised by your doctor. Puncture the vein and secure the venipuncture set with a plaster.
11. Unscrew the syringe to disconnect the vial (**I**).
12. Attach the syringe to the venipuncture set by screwing it clockwise and ensure that no blood enters the syringe (**J**).
13. Remove tourniquet!
14. 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 2 ml/min maximum rate of injection.
15. If a further dose is required, remove the empty syringe by turning it anti-clockwise. Reconstitute the desired amount of product, repeating steps 2. – 9, using a new syringe and connect it to the venipuncture set.
16. 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 KOGENATE Bayer 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 KOGENATE Bayer 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 injection: 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 KOGENATE Bayer is a life-time treatment.

If you use more KOGENATE Bayer 250 IU than you should
No cases of overdose with recombinant coagulation factor VIII have been reported.
If you have used more KOGENATE Bayer 250 IU than you should, please inform your doctor.

If you forget to use KOGENATE Bayer 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 KOGENATE Bayer 250 IU
Do not stop using KOGENATE Bayer without consulting your doctor.

Documentation
It is recommended that every time that you use KOGENATE Bayer, 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 KOGENATE Bayer 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 vial and the pre-filled syringe 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 KOGENATE Bayer 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 KOGENATE Bayer 250 IU looks like and content of the pack

KOGENATE Bayer 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 KOGENATE Bayer 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)
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

KOGENATE Bayer 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 KOGENATE Bayer 500 IU is and what it is used for

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

KOGENATE Bayer is used for treatment and prophylaxis of bleeding in 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.

Each pack of KOGENATE Bayer 500 IU contains a vial with Bio-Set transfer device and a pre-filled syringe with a separate plunger rod, as well as a venipuncture set (for injection into a vein), two alcohol swabs, two dry swabs and two plasters.
The vial contains a dry white to slightly yellow powder or cake. The pre-filled syringe contains 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 KOGENATE Bayer 500 IU

Do not use KOGENATE Bayer 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 KOGENATE Bayer 500 IU.

Take special care with KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer 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.

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

3. How to use KOGENATE Bayer 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 (powder vial with Bio-Set device, pre-filled syringe containing solvent and venipuncture set) for reconstitution and administration that are

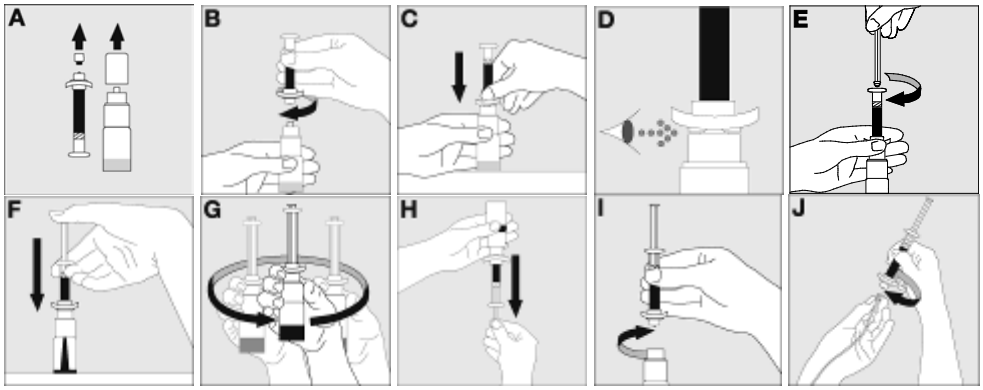
provided with each package of this medicine. If these components cannot be used, please contact your doctor. If any component of the package is opened or damaged, do not use it

- You must filter the reconstituted product before administration to remove potential particulate matter in the solution. Filtering can be achieved by following the reconstitution and/or administration steps as described below. Use the venipuncture set provided as it contains an in-line filter. If you cannot use the venipuncture set provided, use a separate filter which is compatible with KOGENATE Bayer. These compatible filters are luer adaptor-type of Polyacrylic housing with integrated filter element of a Polyamide screen of 5 – 20 micrometer mesh size.

- Do not use the venipuncture set provided for drawing blood because it contains an in-line filter. When you must withdraw blood before an infusion, use an administration set without a filter, then infuse KOGENATE Bayer through an injection filter. If you have any questions about KOGENATE Bayer and compatible separate filters contact your doctor.

- This medicine must **not** be mixed with other infusion solutions. 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. The solution must be prepared on a clean and dry surface.
2. Warm the unopened powder vial and the solvent syringe in your hands until they feel as warm as your hands. The material should not be warmer than body temperature (not exceed 37 °C). Wipe any observable moisture from the vial.
3. Remove the cap from the powder vial by gently moving it from side to side several times, whilst at the same time pulling upwards. Remove the stopper attached to the white cap from the syringe (**A**).
4. Gently screw the syringe on to the powder vial (**B**).
5. Place the vial on a rigid, non-slip surface and hold it firmly with one hand. Then, strongly press down the fingerplate near the syringe tip using your thumb and index finger (**C**) until the finger plate meets the top edge of the Bio-Set. This indicates that the system is activated (**D**).
6. Connect the plunger rod to the syringe by screwing it into the rubber stopper (**E**).
7. Inject the solvent into the vial containing the powder by slowly pushing the syringe plunger down (**F**).
8. Dissolve the powder by gently swirling the vial. Do not shake the vial! Ensure that the powder is completely dissolved before use. Inspect visually for particulate matter and discoloration prior to administration. Do not use solutions that contain visible particles or that are cloudy (**G**).
9. Invert vial/syringe and transfer the solution into syringe by drawing the plunger out slowly and smoothly (**H**). Ensure that the entire contents of the vial are drawn into the syringe.

10. Apply a tourniquet. Determine the point of injection, clean the skin with an alcohol swab, and prepare site of injection antiseptically as advised by your doctor. Puncture the vein and secure the venipuncture set with a plaster.
11. Unscrew the syringe to disconnect the vial (**I**).
12. Attach the syringe to the venipuncture set by screwing it clockwise and ensure that no blood enters the syringe (**J**).
13. Remove tourniquet!
14. 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 2 ml/min maximum rate of injection.
15. If a further dose is required, remove the empty syringe by turning it anti-clockwise. Reconstitute the desired amount of product, repeating steps 2. – 9, using a new syringe and connect it to the venipuncture set.
16. 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 KOGENATE Bayer 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 KOGENATE Bayer 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 injection: 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 KOGENATE Bayer is a life-time treatment.

If you use more KOGENATE Bayer 500 IU than you should
No cases of overdose with recombinant coagulation factor VIII have been reported.
If you have used more KOGENATE Bayer 500 IU than you should, please inform your doctor.

If you forget to use KOGENATE Bayer 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 KOGENATE Bayer 500 IU
Do not stop using KOGENATE Bayer without consulting your doctor.

Documentation
It is recommended that every time that you use KOGENATE Bayer, 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 KOGENATE Bayer 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 vial and the pre-filled syringe 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 KOGENATE Bayer 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 KOGENATE Bayer 500 IU looks like and content of the pack

KOGENATE Bayer 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 KOGENATE Bayer 500 IU.

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Manufacturer
Bayer HealthCare Manufacturing S.r.l.
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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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

Package Leaflet: Information for the user

KOGENATE Bayer 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 KOGENATE Bayer 1000 IU is and what it is used for

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

KOGENATE Bayer is used for treatment and prophylaxis of bleeding in 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.

Each pack of KOGENATE Bayer 1000 IU contains a vial with Bio-Set transfer device and a pre-filled syringe with a separate plunger rod, as well as a venipuncture set (for injection into a vein), two alcohol swabs, two dry swabs and two plasters.
The vial contains a dry white to slightly yellow powder or cake. The pre-filled syringe contains 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 KOGENATE Bayer 1000 IU

Do not use KOGENATE Bayer 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 KOGENATE Bayer 1000 IU.

Take special care with KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer 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.

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

3. How to use KOGENATE Bayer 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 (powder vial with Bio-Set device, pre-filled syringe containing solvent and venipuncture set) for reconstitution and administration that are

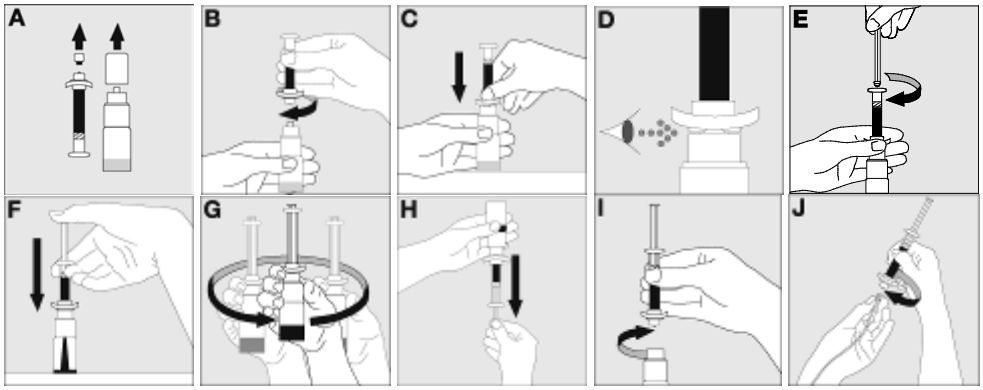
provided with each package of this medicine. If these components cannot be used, please contact your doctor. If any component of the package is opened or damaged, do not use it

- You must filter the reconstituted product before administration to remove potential particulate matter in the solution. Filtering can be achieved by following the reconstitution and/or administration steps as described below. Use the venipuncture set provided as it contains an in-line filter. If you cannot use the venipuncture set provided, use a separate filter which is compatible with KOGENATE Bayer. These compatible filters are luer adaptor-type of Polyacrylic housing with integrated filter element of a Polyamide screen of 5 – 20 micrometer mesh size.

- Do not use the venipuncture set provided for drawing blood because it contains an in-line filter. When you must withdraw blood before an infusion, use an administration set without a filter, then infuse KOGENATE Bayer through an injection filter. If you have any questions about KOGENATE Bayer and compatible separate filters contact your doctor.

- This medicine must **not** be mixed with other infusion solutions. 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. The solution must be prepared on a clean and dry surface.
2. Warm the unopened powder vial and the solvent syringe in your hands until they feel as warm as your hands. The material should not be warmer than body temperature (not exceed 37 °C). Wipe any observable moisture from the vial.
3. Remove the cap from the powder vial by gently moving it from side to side several times, whilst at the same time pulling upwards. Remove the stopper attached to the white cap from the syringe (**A**).
4. Gently screw the syringe on to the powder vial (**B**).
5. Place the vial on a rigid, non-slip surface and hold it firmly with one hand. Then, strongly press down the fingerplate near the syringe tip using your thumb and index finger (**C**) until the finger plate meets the top edge of the Bio-Set. This indicates that the system is activated (**D**).
6. Connect the plunger rod to the syringe by screwing it into the rubber stopper (**E**).
7. Inject the solvent into the vial containing the powder by slowly pushing the syringe plunger down (**F**).
8. Dissolve the powder by gently swirling the vial. Do not shake the vial! Ensure that the powder is completely dissolved before use. Inspect visually for particulate matter and discoloration prior to administration. Do not use solutions that contain visible particles or that are cloudy (**G**).
9. Invert vial/syringe and transfer the solution into syringe by drawing the plunger out slowly and smoothly (**H**). Ensure that the entire contents of the vial are drawn into the syringe.

10. Apply a tourniquet. Determine the point of injection, clean the skin with an alcohol swab, and prepare site of injection antiseptically as advised by your doctor. Puncture the vein and secure the venipuncture set with a plaster.
11. Unscrew the syringe to disconnect the vial (**I**).
12. Attach the syringe to the venipuncture set by screwing it clockwise and ensure that no blood enters the syringe (**J**).
13. Remove tourniquet!
14. 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 2 ml/min maximum rate of injection.
15. If a further dose is required, remove the empty syringe by turning it anti-clockwise. Reconstitute the desired amount of product, repeating steps 2. – 9, using a new syringe and connect it to the venipuncture set.
16. 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 KOGENATE Bayer 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 KOGENATE Bayer 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 injection: 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 KOGENATE Bayer is a life-time treatment.

If you use more KOGENATE Bayer 1000 IU than you should
No cases of overdose with recombinant coagulation factor VIII have been reported.
If you have used more KOGENATE Bayer 1000 IU than you should, please inform your doctor.

If you forget to use KOGENATE Bayer 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 KOGENATE Bayer 1000 IU
Do not stop using KOGENATE Bayer without consulting your doctor.

Documentation
It is recommended that every time that you use KOGENATE Bayer, 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 KOGENATE Bayer 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 vial and the pre-filled syringe 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 KOGENATE Bayer 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 KOGENATE Bayer 1000 IU looks like and content of the pack

KOGENATE Bayer 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 KOGENATE Bayer 1000 IU.

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

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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

Package Leaflet: Information for the user

KOGENATE Bayer 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 KOGENATE Bayer 2000 IU is and what it is used for

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

KOGENATE Bayer is used for treatment and prophylaxis of bleeding in 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.

Each pack of KOGENATE Bayer 2000 IU contains a vial with Bio-Set transfer device and a pre-filled syringe with a separate plunger rod, as well as a venipuncture set (for injection into a vein), two alcohol swabs, two dry swabs and two plasters.
The vial contains a dry white to slightly yellow powder or cake. The pre-filled syringe contains 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 KOGENATE Bayer 2000 IU

Do not use KOGENATE Bayer 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 KOGENATE Bayer 2000 IU.

Take special care with KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer 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.

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

3. How to use KOGENATE Bayer 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 (powder vial with Bio-Set device, pre-filled syringe containing solvent and venipuncture set) for reconstitution and administration that are

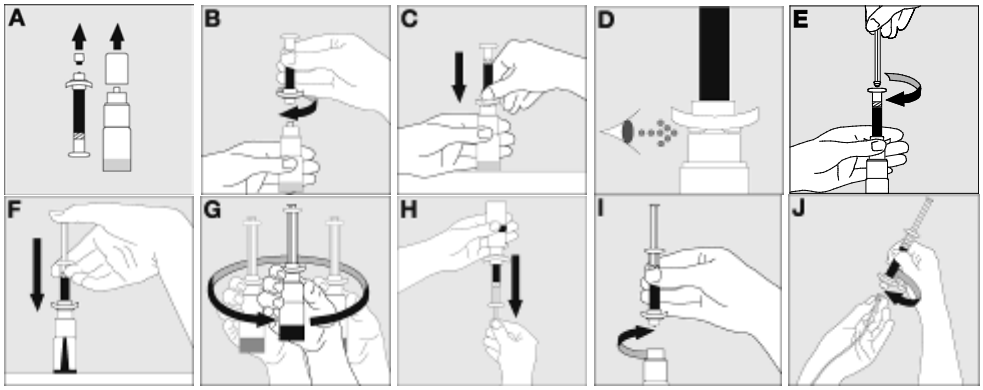
provided with each package of this medicine. If these components cannot be used, please contact your doctor. If any component of the package is opened or damaged, do not use it

- You must filter the reconstituted product before administration to remove potential particulate matter in the solution. Filtering can be achieved by following the reconstitution and/or administration steps as described below. Use the venipuncture set provided as it contains an in-line filter. If you cannot use the venipuncture set provided, use a separate filter which is compatible with KOGENATE Bayer. These compatible filters are luer adaptor-type of Polyacrylic housing with integrated filter element of a Polyamide screen of 5 – 20 micrometer mesh size.

- Do not use the venipuncture set provided for drawing blood because it contains an in-line filter. When you must withdraw blood before an infusion, use an administration set without a filter, then infuse KOGENATE Bayer through an injection filter. If you have any questions about KOGENATE Bayer and compatible separate filters contact your doctor.

- This medicine must **not** be mixed with other infusion solutions. 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. The solution must be prepared on a clean and dry surface.
2. Warm the unopened powder vial and the solvent syringe in your hands until they feel as warm as your hands. The material should not be warmer than body temperature (not exceed 37 °C). Wipe any observable moisture from the vial.
3. Remove the cap from the powder vial by gently moving it from side to side several times, whilst at the same time pulling upwards. Remove the stopper attached to the white cap from the syringe (**A**).
4. Gently screw the syringe on to the powder vial (**B**).
5. Place the vial on a rigid, non-slip surface and hold it firmly with one hand. Then, strongly press down the fingerplate near the syringe tip using your thumb and index finger (**C**) until the finger plate meets the top edge of the Bio-Set. This indicates that the system is activated (**D**).
6. Connect the plunger rod to the syringe by screwing it into the rubber stopper (**E**).
7. Inject the solvent into the vial containing the powder by slowly pushing the syringe plunger down (**F**).
8. Dissolve the powder by gently swirling the vial. Do not shake the vial! Ensure that the powder is completely dissolved before use. Inspect visually for particulate matter and discoloration prior to administration. Do not use solutions that contain visible particles or that are cloudy (**G**).
9. Invert vial/syringe and transfer the solution into syringe by drawing the plunger out slowly and smoothly (**H**). Ensure that the entire contents of the vial are drawn into the syringe.

10. Apply a tourniquet. Determine the point of injection, clean the skin with an alcohol swab, and prepare site of injection antiseptically as advised by your doctor. Puncture the vein and secure the venipuncture set with a plaster.
11. Unscrew the syringe to disconnect the vial (**I**).
12. Attach the syringe to the venipuncture set by screwing it clockwise and ensure that no blood enters the syringe (**J**).
13. Remove tourniquet!
14. 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 2 ml/min maximum rate of injection.
15. If a further dose is required, remove the empty syringe by turning it anti-clockwise. Reconstitute the desired amount of product, repeating steps 2. – 9, using a new syringe and connect it to the venipuncture set.
16. 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 KOGENATE Bayer 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 KOGENATE Bayer 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 injection: 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 KOGENATE Bayer is a life-time treatment.

If you use more KOGENATE Bayer 2000 IU than you should
No cases of overdose with recombinant coagulation factor VIII have been reported.
If you have used more KOGENATE Bayer 2000 IU than you should, please inform your doctor.

If you forget to use KOGENATE Bayer 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 KOGENATE Bayer 2000 IU
Do not stop using KOGENATE Bayer without consulting your doctor.

Documentation
It is recommended that every time that you use KOGENATE Bayer, 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 KOGENATE Bayer 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 vial and the pre-filled syringe 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 KOGENATE Bayer 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 KOGENATE Bayer 2000 IU looks like and content of the pack

KOGENATE Bayer 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 KOGENATE Bayer 2000 IU.

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13342 Berlin
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Manufacturer
Bayer HealthCare Manufacturing S.r.l.
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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

KOGENATE Bayer 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 KOGENATE Bayer 3000 IU is and what it is used for

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

KOGENATE Bayer is used for treatment and prophylaxis of bleeding in 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.

Each pack of KOGENATE Bayer 3000 IU contains a vial with Bio-Set transfer device and a pre-filled syringe with a separate plunger rod, as well as a venipuncture set (for injection into a vein), two alcohol swabs, two dry swabs and two plasters.
The vial contains a dry white to slightly yellow powder or cake. The pre-filled syringe contains 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 KOGENATE Bayer 3000 IU

Do not use KOGENATE Bayer 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 KOGENATE Bayer 3000 IU.

Take special care with KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer 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.

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

3. How to use KOGENATE Bayer 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 (powder vial with Bio-Set device, pre-filled syringe containing solvent and venipuncture set) for reconstitution and administration that are

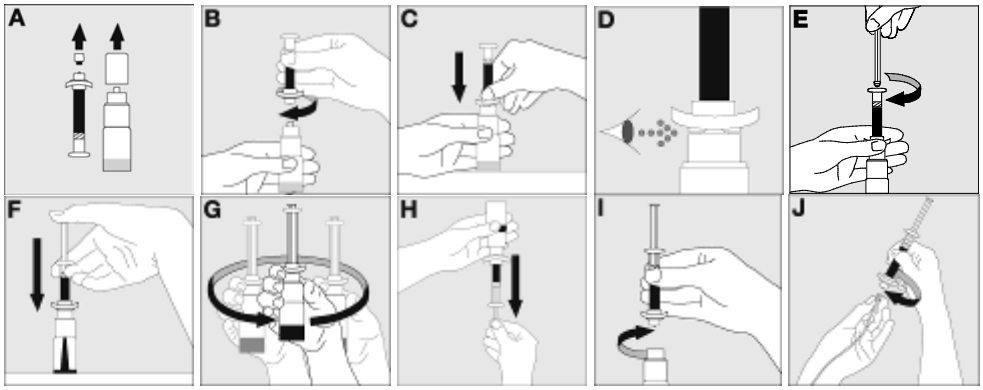
provided with each package of this medicine. If these components cannot be used, please contact your doctor. If any component of the package is opened or damaged, do not use it

- You must filter the reconstituted product before administration to remove potential particulate matter in the solution. Filtering can be achieved by following the reconstitution and/or administration steps as described below. Use the venipuncture set provided as it contains an in-line filter. If you cannot use the venipuncture set provided, use a separate filter which is compatible with KOGENATE Bayer. These compatible filters are luer adaptor-type of Polyacrylic housing with integrated filter element of a Polyamide screen of 5 – 20 micrometer mesh size.

- Do not use the venipuncture set provided for drawing blood because it contains an in-line filter. When you must withdraw blood before an infusion, use an administration set without a filter, then infuse KOGENATE Bayer through an injection filter. If you have any questions about KOGENATE Bayer and compatible separate filters contact your doctor.

- This medicine must **not** be mixed with other infusion solutions. 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. The solution must be prepared on a clean and dry surface.
2. Warm the unopened powder vial and the solvent syringe in your hands until they feel as warm as your hands. The material should not be warmer than body temperature (not exceed 37 °C). Wipe any observable moisture from the vial.
3. Remove the cap from the powder vial by gently moving it from side to side several times, whilst at the same time pulling upwards. Remove the stopper attached to the white cap from the syringe (**A**).
4. Gently screw the syringe on to the powder vial (**B**).
5. Place the vial on a rigid, non-slip surface and hold it firmly with one hand. Then, strongly press down the fingerplate near the syringe tip using your thumb and index finger (**C**) until the finger plate meets the top edge of the Bio-Set. This indicates that the system is activated (**D**).
6. Connect the plunger rod to the syringe by screwing it into the rubber stopper (**E**).
7. Inject the solvent into the vial containing the powder by slowly pushing the syringe plunger down (**F**).
8. Dissolve the powder by gently swirling the vial. Do not shake the vial! Ensure that the powder is completely dissolved before use. Inspect visually for particulate matter and discoloration prior to administration. Do not use solutions that contain visible particles or that are cloudy (**G**).
9. Invert vial/syringe and transfer the solution into syringe by drawing the plunger out slowly and smoothly (**H**). Ensure that the entire contents of the vial are drawn into the syringe.

10. Apply a tourniquet. Determine the point of injection, clean the skin with an alcohol swab, and prepare site of injection antiseptically as advised by your doctor. Puncture the vein and secure the venipuncture set with a plaster.
11. Unscrew the syringe to disconnect the vial (**I**).
12. Attach the syringe to the venipuncture set by screwing it clockwise and ensure that no blood enters the syringe (**J**).
13. Remove tourniquet!
14. 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 2 ml/min maximum rate of injection.
15. If a further dose is required, remove the empty syringe by turning it anti-clockwise. Reconstitute the desired amount of product, repeating steps 2. – 9, using a new syringe and connect it to the venipuncture set.
16. 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 KOGENATE Bayer 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 KOGENATE Bayer 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 injection: 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 KOGENATE Bayer is a life-time treatment.

If you use more KOGENATE Bayer 3000 IU than you should
No cases of overdose with recombinant coagulation factor VIII have been reported.
If you have used more KOGENATE Bayer 3000 IU than you should, please inform your doctor.

If you forget to use KOGENATE Bayer 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 KOGENATE Bayer 3000 IU
Do not stop using KOGENATE Bayer without consulting your doctor.

Documentation
It is recommended that every time that you use KOGENATE Bayer, 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 KOGENATE Bayer 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 vial and the pre-filled syringe 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.

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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 KOGENATE Bayer 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 KOGENATE Bayer 3000 IU looks like and content of the pack

KOGENATE Bayer 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 KOGENATE Bayer 3000 IU.

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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

Package Leaflet: Information for the user

KOGENATE Bayer 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 KOGENATE Bayer 250 IU is and what it is used for

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

KOGENATE Bayer is used for treatment and prophylaxis of bleeding in 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.

Each pack of KOGENATE Bayer 250 IU contains a vial and a pre-filled syringe with a separate plunger rod, as well as a vial adapter, a venipuncture set (for injection into a vein), two alcohol swabs, two dry swabs and two plasters.
The vial contains a dry white to slightly yellow powder or cake. The pre-filled syringe contains 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 KOGENATE Bayer 250 IU

Do not use KOGENATE Bayer 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 KOGENATE Bayer 250 IU.

Take special care with KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer 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.

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

3. How to use KOGENATE Bayer 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.

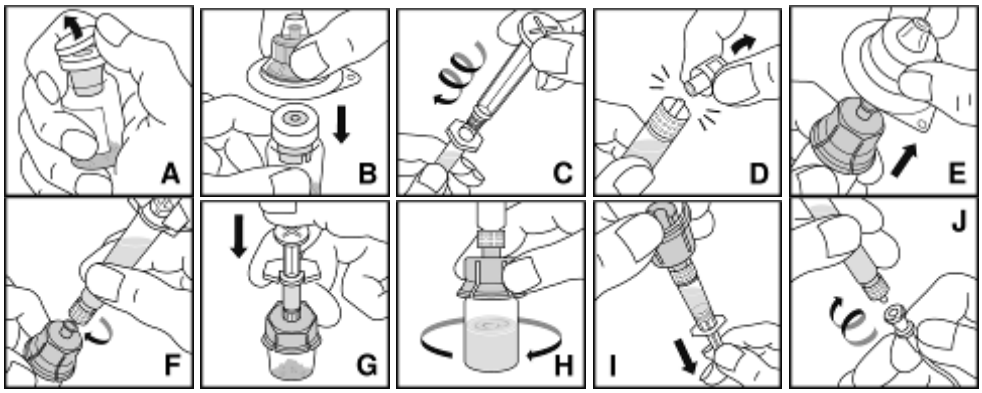
- You must use aseptic conditions (meaning clean and germ free) during reconstitution and administration. Use only the medical devices (vial adapter, pre-filled syringe containing solvent and venipuncture set) for reconstitution and administration that are provided with each package of this medicine. If a package is opened or damaged, do not use this medical

device. 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 vial adapter.**

- This medicine must **not** be mixed with other infusion solutions. 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 vial and syringe in your hands to a comfortable temperature (do not exceed 37 °C).
3. Remove protective cap from the vial (A) then clean the rubber stopper with a sterile swab (or use an antiseptic spray).
4. Place product vial on a firm, non-skid surface. Peel off the paper cover on the vial adapter plastic housing. Do not remove the adapter from the plastic housing. Holding the adapter housing, place over the product vial and firmly press down (B). The adapter will snap over the vial cap. Do not remove the adapter housing at this step.
5. Hold the pre-filled sterile water for injection (SWFI) syringe upright, grasp the plunger rod per the diagram and attach the rod by turning it firmly clockwise into the threaded stopper (C).
6. Holding the syringe by the barrel, snap the syringe cap off the tip (D). Do not touch the syringe tip with your hand or any surface. Set the syringe aside for further use.
7. Now remove and discard the adapter housing (E).
8. Attach the pre-filled syringe to the threaded vial adapter by turning clockwise (F).
9. Inject the diluent by slowly pushing down on the plunger rod (G).
10. Swirl vial gently until all material is dissolved (H). Do not shake vial. Be sure that the powder is completely dissolved. Inspect visually for particulate matter and discoloration prior to administration. Do not use solutions containing visible particles or that are cloudy.
11. Hold the vial on end above the vial adapter and syringe (I). Fill the syringe by drawing the plunger out slowly and smoothly. Ensure that the entire content of the vial is drawn into the syringe.
12. Apply a tourniquet.
13. Determine the point of injection and prepare antiseptically
14. Puncture the vein and secure the venipuncture set with a plaster.
15. Holding the plunger in place, remove the syringe from the vial adapter (the latter should remain attached to the vial). Attach the syringe to the venipuncture set and ensure that no blood enters the syringe (J).
16. Remove tourniquet.
17. 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.

18. If a further dose needs to be administered, use a new syringe with product reconstituted as described above.
19. If no further dose is required, remove the venipuncture set and syringe. Hold a swab firmly over the injection site on the outstretched arm for approx. 2 minutes. Finally, apply a small pressure dressing to the wound.

Treatment of bleeding
How much KOGENATE Bayer 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 KOGENATE Bayer 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 injection: 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 KOGENATE Bayer is a life-time treatment.

If you use more KOGENATE Bayer 250 IU than you should
No cases of overdose with recombinant coagulation factor VIII have been reported.
If you have used more KOGENATE Bayer 250 IU than you should, please inform your doctor.

If you forget to use KOGENATE Bayer 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 KOGENATE Bayer 250 IU
Do not stop using KOGENATE Bayer without consulting your doctor.

Documentation
It is recommended that every time that you use KOGENATE Bayer, 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 KOGENATE Bayer 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 vial and the pre-filled syringe 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 KOGENATE Bayer 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 KOGENATE Bayer 250 IU looks like and content of the pack

KOGENATE Bayer 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 KOGENATE Bayer 250 IU.

Marketing Authorisation Holder
Bayer Pharma AG
13342 Berlin
Germany

Manufacturer
Bayer HealthCare Manufacturing S.r.l.
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20024 Garbagnate Milanese (MI)
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For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

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Package Leaflet: Information for the user

KOGENATE Bayer 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 KOGENATE Bayer 500 IU is and what it is used for

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

KOGENATE Bayer is used for treatment and prophylaxis of bleeding in 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.

Each pack of KOGENATE Bayer 500 IU contains a vial and a pre-filled syringe with a separate plunger rod, as well as a vial adapter, a venipuncture set (for injection into a vein), two alcohol swabs, two dry swabs and two plasters.
The vial contains a dry white to slightly yellow powder or cake. The pre-filled syringe contains 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 KOGENATE Bayer 500 IU

Do not use KOGENATE Bayer 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 KOGENATE Bayer 500 IU.

Take special care with KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer 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.

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

3. How to use KOGENATE Bayer 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.

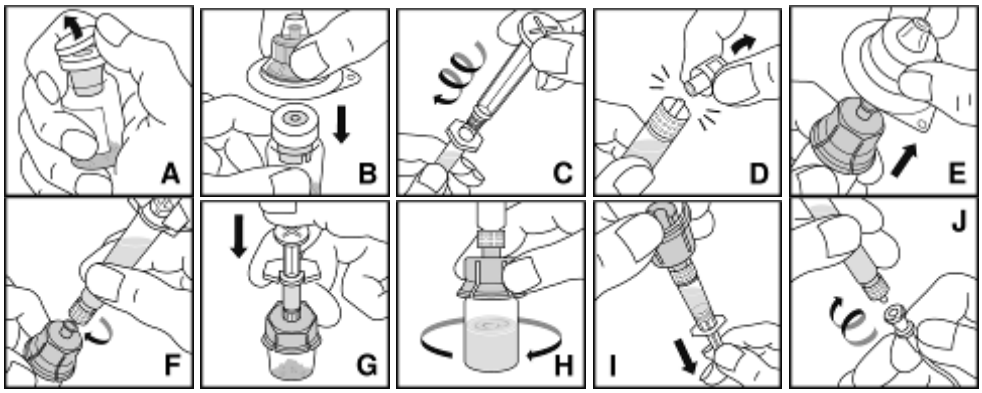
- You must use aseptic conditions (meaning clean and germ free) during reconstitution and administration. Use only the medical devices (vial adapter, pre-filled syringe containing solvent and venipuncture set) for reconstitution and administration that are provided with each package of this medicine. If a package is opened or damaged, do not use this medical

device. 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 vial adapter.**

- This medicine must **not** be mixed with other infusion solutions. 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 vial and syringe in your hands to a comfortable temperature (do not exceed 37 °C).
3. Remove protective cap from the vial (A) then clean the rubber stopper with a sterile swab (or use an antiseptic spray).
4. Place product vial on a firm, non-skid surface. Peel off the paper cover on the vial adapter plastic housing. Do not remove the adapter from the plastic housing. Holding the adapter housing, place over the product vial and firmly press down (B). The adapter will snap over the vial cap. Do not remove the adapter housing at this step.
5. Hold the pre-filled sterile water for injection (SWFI) syringe upright, grasp the plunger rod per the diagram and attach the rod by turning it firmly clockwise into the threaded stopper (C).
6. Holding the syringe by the barrel, snap the syringe cap off the tip (D). Do not touch the syringe tip with your hand or any surface. Set the syringe aside for further use.
7. Now remove and discard the adapter housing (E).
8. Attach the pre-filled syringe to the threaded vial adapter by turning clockwise (F).
9. Inject the diluent by slowly pushing down on the plunger rod (G).
10. Swirl vial gently until all material is dissolved (H). Do not shake vial. Be sure that the powder is completely dissolved. Inspect visually for particulate matter and discoloration prior to administration. Do not use solutions containing visible particles or that are cloudy.
11. Hold the vial on end above the vial adapter and syringe (I). Fill the syringe by drawing the plunger out slowly and smoothly. Ensure that the entire content of the vial is drawn into the syringe.
12. Apply a tourniquet.
13. Determine the point of injection and prepare antiseptically
14. Puncture the vein and secure the venipuncture set with a plaster.
15. Holding the plunger in place, remove the syringe from the vial adapter (the latter should remain attached to the vial). Attach the syringe to the venipuncture set and ensure that no blood enters the syringe (J).
16. Remove tourniquet.
17. 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.

18. If a further dose needs to be administered, use a new syringe with product reconstituted as described above.
19. If no further dose is required, remove the venipuncture set and syringe. Hold a swab firmly over the injection site on the outstretched arm for approx. 2 minutes. Finally, apply a small pressure dressing to the wound.

Treatment of bleeding
How much KOGENATE Bayer 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 KOGENATE Bayer 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 injection: 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 KOGENATE Bayer is a life-time treatment.

If you use more KOGENATE Bayer 500 IU than you should
No cases of overdose with recombinant coagulation factor VIII have been reported.
If you have used more KOGENATE Bayer 500 IU than you should, please inform your doctor.

If you forget to use KOGENATE Bayer 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 KOGENATE Bayer 500 IU
Do not stop using KOGENATE Bayer without consulting your doctor.

Documentation
It is recommended that every time that you use KOGENATE Bayer, 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 KOGENATE Bayer 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 vial and the pre-filled syringe 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 KOGENATE Bayer 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 KOGENATE Bayer 500 IU looks like and content of the pack

KOGENATE Bayer 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 KOGENATE Bayer 500 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

Package Leaflet: Information for the user

KOGENATE Bayer 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 KOGENATE Bayer 1000 IU is and what it is used for

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

KOGENATE Bayer is used for treatment and prophylaxis of bleeding in 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.

Each pack of KOGENATE Bayer 1000 IU contains a vial and a pre-filled syringe with a separate plunger rod, as well as a vial adapter, a venipuncture set (for injection into a vein), two alcohol swabs, two dry swabs and two plasters.
The vial contains a dry white to slightly yellow powder or cake. The pre-filled syringe contains 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 KOGENATE Bayer 1000 IU

Do not use KOGENATE Bayer 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 KOGENATE Bayer 1000 IU.

Take special care with KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer 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.

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

3. How to use KOGENATE Bayer 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.

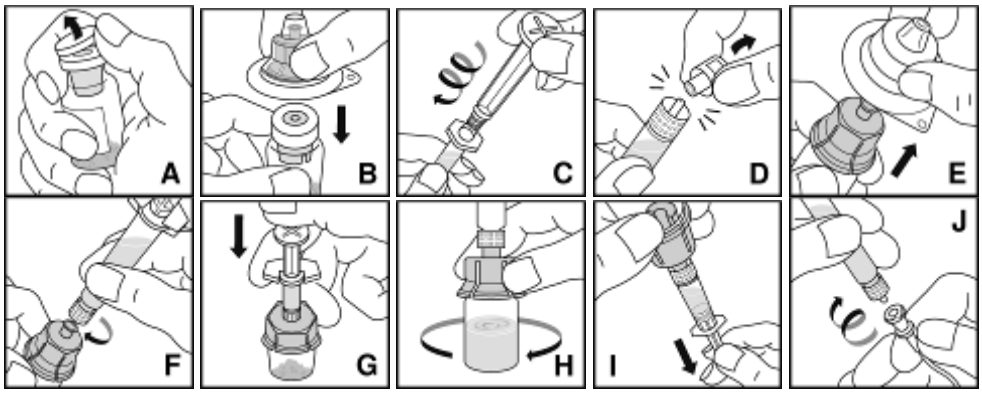
- You must use aseptic conditions (meaning clean and germ free) during reconstitution and administration. Use only the medical devices (vial adapter, pre-filled syringe containing solvent and venipuncture set) for reconstitution and administration that are provided with each package of this medicine. If a package is opened or damaged, do not use this medical

device. 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 vial adapter.**

- This medicine must **not** be mixed with other infusion solutions. 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 vial and syringe in your hands to a comfortable temperature (do not exceed 37 °C).
3. Remove protective cap from the vial (A) then clean the rubber stopper with a sterile swab (or use an antiseptic spray).
4. Place product vial on a firm, non-skid surface. Peel off the paper cover on the vial adapter plastic housing. Do not remove the adapter from the plastic housing. Holding the adapter housing, place over the product vial and firmly press down (B). The adapter will snap over the vial cap. Do not remove the adapter housing at this step.
5. Hold the pre-filled sterile water for injection (SWFI) syringe upright, grasp the plunger rod per the diagram and attach the rod by turning it firmly clockwise into the threaded stopper (C).
6. Holding the syringe by the barrel, snap the syringe cap off the tip (D). Do not touch the syringe tip with your hand or any surface. Set the syringe aside for further use.
7. Now remove and discard the adapter housing (E).
8. Attach the pre-filled syringe to the threaded vial adapter by turning clockwise (F).
9. Inject the diluent by slowly pushing down on the plunger rod (G).
10. Swirl vial gently until all material is dissolved (H). Do not shake vial. Be sure that the powder is completely dissolved. Inspect visually for particulate matter and discoloration prior to administration. Do not use solutions containing visible particles or that are cloudy.
11. Hold the vial on end above the vial adapter and syringe (I). Fill the syringe by drawing the plunger out slowly and smoothly. Ensure that the entire content of the vial is drawn into the syringe.
12. Apply a tourniquet.
13. Determine the point of injection and prepare antiseptically
14. Puncture the vein and secure the venipuncture set with a plaster.
15. Holding the plunger in place, remove the syringe from the vial adapter (the latter should remain attached to the vial). Attach the syringe to the venipuncture set and ensure that no blood enters the syringe (J).
16. Remove tourniquet.
17. 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.

18. If a further dose needs to be administered, use a new syringe with product reconstituted as described above.
19. If no further dose is required, remove the venipuncture set and syringe. Hold a swab firmly over the injection site on the outstretched arm for approx. 2 minutes. Finally, apply a small pressure dressing to the wound.

Treatment of bleeding
How much KOGENATE Bayer 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 KOGENATE Bayer 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 injection: 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 KOGENATE Bayer is a life-time treatment.

If you use more KOGENATE Bayer 1000 IU than you should
No cases of overdose with recombinant coagulation factor VIII have been reported.
If you have used more KOGENATE Bayer 1000 IU than you should, please inform your doctor.

If you forget to use KOGENATE Bayer 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 KOGENATE Bayer 1000 IU
Do not stop using KOGENATE Bayer without consulting your doctor.

Documentation
It is recommended that every time that you use KOGENATE Bayer, 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 KOGENATE Bayer 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 vial and the pre-filled syringe 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 KOGENATE Bayer 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 KOGENATE Bayer 1000 IU looks like and content of the pack

KOGENATE Bayer 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 KOGENATE Bayer 1000 IU.

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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

Package Leaflet: Information for the user

KOGENATE Bayer 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 KOGENATE Bayer 2000 IU is and what it is used for

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

KOGENATE Bayer is used for treatment and prophylaxis of bleeding in 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.

Each pack of KOGENATE Bayer 2000 IU contains a vial and a pre-filled syringe with a separate plunger rod, as well as a vial adapter, a venipuncture set (for injection into a vein), two alcohol swabs, two dry swabs and two plasters.
The vial contains a dry white to slightly yellow powder or cake. The pre-filled syringe contains 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 KOGENATE Bayer 2000 IU

Do not use KOGENATE Bayer 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 KOGENATE Bayer 2000 IU.

Take special care with KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer 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.

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

3. How to use KOGENATE Bayer 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.

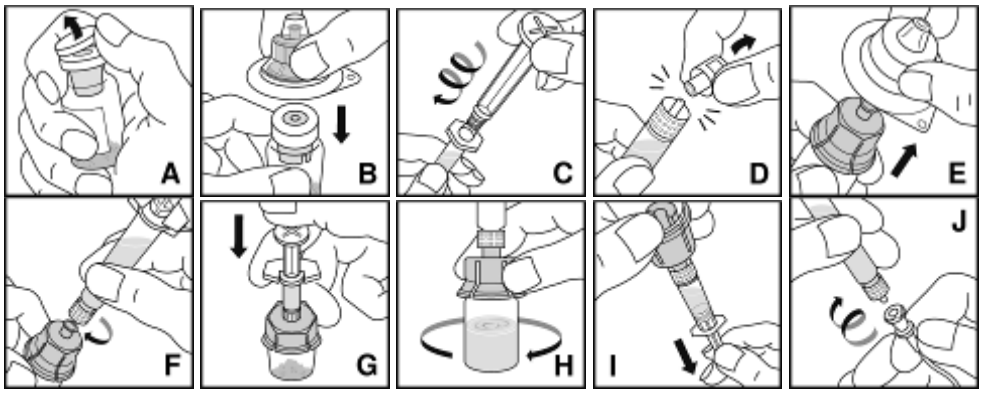
- You must use aseptic conditions (meaning clean and germ free) during reconstitution and administration. Use only the medical devices (vial adapter, pre-filled syringe containing solvent and venipuncture set) for reconstitution and administration that are provided with each package of this medicine. If a package is opened or damaged, do not use this medical

device. 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 vial adapter.**

- This medicine must **not** be mixed with other infusion solutions. 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 vial and syringe in your hands to a comfortable temperature (do not exceed 37 °C).
3. Remove protective cap from the vial (A) then clean the rubber stopper with a sterile swab (or use an antiseptic spray).
4. Place product vial on a firm, non-skid surface. Peel off the paper cover on the vial adapter plastic housing. Do not remove the adapter from the plastic housing. Holding the adapter housing, place over the product vial and firmly press down (B). The adapter will snap over the vial cap. Do not remove the adapter housing at this step.
5. Hold the pre-filled sterile water for injection (SWFI) syringe upright, grasp the plunger rod per the diagram and attach the rod by turning it firmly clockwise into the threaded stopper (C).
6. Holding the syringe by the barrel, snap the syringe cap off the tip (D). Do not touch the syringe tip with your hand or any surface. Set the syringe aside for further use.
7. Now remove and discard the adapter housing (E).
8. Attach the pre-filled syringe to the threaded vial adapter by turning clockwise (F).
9. Inject the diluent by slowly pushing down on the plunger rod (G).
10. Swirl vial gently until all material is dissolved (H). Do not shake vial. Be sure that the powder is completely dissolved. Inspect visually for particulate matter and discoloration prior to administration. Do not use solutions containing visible particles or that are cloudy.
11. Hold the vial on end above the vial adapter and syringe (I). Fill the syringe by drawing the plunger out slowly and smoothly. Ensure that the entire content of the vial is drawn into the syringe.
12. Apply a tourniquet.
13. Determine the point of injection and prepare antiseptically
14. Puncture the vein and secure the venipuncture set with a plaster.
15. Holding the plunger in place, remove the syringe from the vial adapter (the latter should remain attached to the vial). Attach the syringe to the venipuncture set and ensure that no blood enters the syringe (J).
16. Remove tourniquet.
17. 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.

18. If a further dose needs to be administered, use a new syringe with product reconstituted as described above.
19. If no further dose is required, remove the venipuncture set and syringe. Hold a swab firmly over the injection site on the outstretched arm for approx. 2 minutes. Finally, apply a small pressure dressing to the wound.

Treatment of bleeding
How much KOGENATE Bayer 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 KOGENATE Bayer 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 injection: 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 KOGENATE Bayer is a life-time treatment.

If you use more KOGENATE Bayer 2000 IU than you should
No cases of overdose with recombinant coagulation factor VIII have been reported.
If you have used more KOGENATE Bayer 2000 IU than you should, please inform your doctor.

If you forget to use KOGENATE Bayer 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 KOGENATE Bayer 2000 IU
Do not stop using KOGENATE Bayer without consulting your doctor.

Documentation
It is recommended that every time that you use KOGENATE Bayer, 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 KOGENATE Bayer 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 vial and the pre-filled syringe 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 KOGENATE Bayer 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 KOGENATE Bayer 2000 IU looks like and content of the pack

KOGENATE Bayer 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 KOGENATE Bayer 2000 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

KOGENATE Bayer 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 KOGENATE Bayer 3000 IU is and what it is used for

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

KOGENATE Bayer is used for treatment and prophylaxis of bleeding in 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.

Each pack of KOGENATE Bayer 3000 IU contains a vial and a pre-filled syringe with a separate plunger rod, as well as a vial adapter, a venipuncture set (for injection into a vein), two alcohol swabs, two dry swabs and two plasters.
The vial contains a dry white to slightly yellow powder or cake. The pre-filled syringe contains 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 KOGENATE Bayer 3000 IU

Do not use KOGENATE Bayer 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 KOGENATE Bayer 3000 IU.

Take special care with KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer 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 KOGENATE Bayer 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.

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

3. How to use KOGENATE Bayer 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.

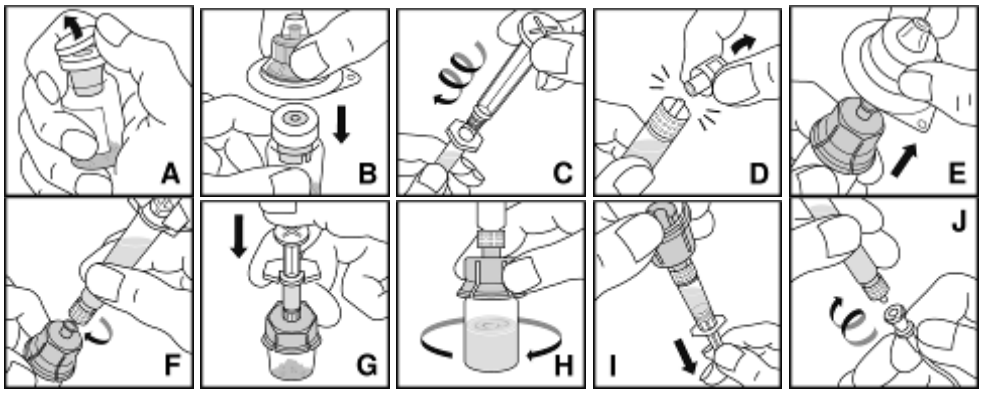
- You must use aseptic conditions (meaning clean and germ free) during reconstitution and administration. Use only the medical devices (vial adapter, pre-filled syringe containing solvent and venipuncture set) for reconstitution and administration that are provided with each package of this medicine. If a package is opened or damaged, do not use this medical

device. 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 vial adapter.**

- This medicine must **not** be mixed with other infusion solutions. 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 vial and syringe in your hands to a comfortable temperature (do not exceed 37 °C).
3. Remove protective cap from the vial (A) then clean the rubber stopper with a sterile swab (or use an antiseptic spray).
4. Place product vial on a firm, non-skid surface. Peel off the paper cover on the vial adapter plastic housing. Do not remove the adapter from the plastic housing. Holding the adapter housing, place over the product vial and firmly press down (B). The adapter will snap over the vial cap. Do not remove the adapter housing at this step.
5. Hold the pre-filled sterile water for injection (SWFI) syringe upright, grasp the plunger rod per the diagram and attach the rod by turning it firmly clockwise into the threaded stopper (C).
6. Holding the syringe by the barrel, snap the syringe cap off the tip (D). Do not touch the syringe tip with your hand or any surface. Set the syringe aside for further use.
7. Now remove and discard the adapter housing (E).
8. Attach the pre-filled syringe to the threaded vial adapter by turning clockwise (F).
9. Inject the diluent by slowly pushing down on the plunger rod (G).
10. Swirl vial gently until all material is dissolved (H). Do not shake vial. Be sure that the powder is completely dissolved. Inspect visually for particulate matter and discoloration prior to administration. Do not use solutions containing visible particles or that are cloudy.
11. Hold the vial on end above the vial adapter and syringe (I). Fill the syringe by drawing the plunger out slowly and smoothly. Ensure that the entire content of the vial is drawn into the syringe.
12. Apply a tourniquet.
13. Determine the point of injection and prepare antiseptically
14. Puncture the vein and secure the venipuncture set with a plaster.
15. Holding the plunger in place, remove the syringe from the vial adapter (the latter should remain attached to the vial). Attach the syringe to the venipuncture set and ensure that no blood enters the syringe (J).
16. Remove tourniquet.
17. 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.

18. If a further dose needs to be administered, use a new syringe with product reconstituted as described above.
19. If no further dose is required, remove the venipuncture set and syringe. Hold a swab firmly over the injection site on the outstretched arm for approx. 2 minutes. Finally, apply a small pressure dressing to the wound.

Treatment of bleeding
How much KOGENATE Bayer 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 KOGENATE Bayer 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 injection: 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 KOGENATE Bayer is a life-time treatment.

If you use more KOGENATE Bayer 3000 IU than you should
No cases of overdose with recombinant coagulation factor VIII have been reported.
If you have used more KOGENATE Bayer 3000 IU than you should, please inform your doctor.

If you forget to use KOGENATE Bayer 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 KOGENATE Bayer 3000 IU
Do not stop using KOGENATE Bayer without consulting your doctor.

Documentation
It is recommended that every time that you use KOGENATE Bayer, 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 KOGENATE Bayer 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 vial and the pre-filled syringe 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 KOGENATE Bayer 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 KOGENATE Bayer 3000 IU looks like and content of the pack

KOGENATE Bayer 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 KOGENATE Bayer 3000 IU.

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