ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
1. NAME OF THE MEDICINAL PRODUCT

KOGENATE Bayer 250 IU powder and solvent for solution for injection
KOGENATE Bayer 500 IU powder and solvent for solution for injection
KOGENATE Bayer 1000 IU powder and solvent for solution for injection
KOGENATE Bayer 2000 IU powder and solvent for solution for injection
KOGENATE Bayer 3000 IU powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION


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

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

The potency (IU) is determined using the one-stage clotting assay against the FDA Mega standard which was calibrated against WHO standard in International Units (IU).

The specific activity of KOGENATE Bayer is approximately 4000 IU/mg protein.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection (Bio-Set System).

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). This preparation does not contain von Willebrand factor and is therefore not indicated in von Willebrand's disease.
This product is indicated for adults, adolescents and children of all ages.

4.2 Posology and method of administration

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

Posology

The number of units of factor VIII administered is expressed in International Units (IU), which are related to the current WHO standard for factor VIII products. Factor VIII activity in plasma is expressed either as a percentage (relative to normal human plasma) or in International Units (relative to the International Standard for factor VIII in plasma).

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

On demand treatment

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

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

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

The dose, frequency and duration of the substitution therapy must be individualised according to the patient's needs (weight, severity of disorder of the haemostatic function, the site and extent of the bleeding, the presence of inhibitors, and the factor VIII level desired).
The following table provides a guide for factor VIII minimum blood levels. In the case of the haemorrhagic events listed, the factor VIII activity should not fall below the given level (in % of normal) in the corresponding period:

Table 1: Guide for dosing in bleeding episodes and surgery

<table>
<thead>
<tr>
<th>Degree of haemorrhage/ Type of surgical procedure</th>
<th>Factor VIII level required (%) (IU/dl)</th>
<th>Frequency of doses (hours)/ Duration of therapy (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemorrhage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early haemarthrosis, muscle bleed or oral bleed</td>
<td>20 - 40</td>
<td>Repeat every 12 to 24 hours. At least 1 day, until the bleeding episode as indicated by pain is resolved or healing is achieved.</td>
</tr>
<tr>
<td>More extensive haemarthrosis, muscle bleed or haematoma</td>
<td>30 - 60</td>
<td>Repeat infusion every 12 - 24 hours for 3 - 4 days or more until pain and disability are resolved.</td>
</tr>
<tr>
<td>Life threatening haemorrhages (such as intracranial bleed, throat bleed, severe abdominal bleed)</td>
<td>60 - 100</td>
<td>Repeat infusion every 8 to 24 hours until threat is resolved</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor including tooth extraction</td>
<td>30 - 60</td>
<td>Every 24 hours, at least 1 day, until healing is achieved.</td>
</tr>
</tbody>
</table>
| Major (pre- and postoperative)                    | 80 - 100                                | 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 presurgery 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.

\[
\text{Infusion rate (in IU/kg/h)} = \text{Clearance (in mL/h/kg)} \times \text{desired factor VIII level (in IU/mL)}
\]

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.

Special populations

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 2 to 5 minutes. The rate of administration should be determined by the patient’s comfort level (maximal rate of infusion: 2 mL/min).

Continuous infusion

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).
Table 2: Example for calculation of infusion rate for continuous infusion after initial bolus injection

<table>
<thead>
<tr>
<th></th>
<th>Desired plasma FVIII level</th>
<th>Infusion rate IU/h/kg</th>
<th>Infusion rate for 75 kg patient mL/h</th>
<th>Concentrations of rFVIII solution IU/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clearance: 3 mL/h/kg</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>100 % (1 IU/mL)</td>
<td>3.0</td>
<td>2.25</td>
<td>1.125</td>
<td>0.56</td>
</tr>
<tr>
<td>60 % (0.6 IU/mL)</td>
<td>1.8</td>
<td>1.35</td>
<td>0.68</td>
<td>0.34</td>
</tr>
<tr>
<td>40 % (0.4 IU/mL)</td>
<td>1.2</td>
<td>0.9</td>
<td>0.45</td>
<td>0.225</td>
</tr>
</tbody>
</table>

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

Cases of recurrent inhibitor (low titre) have been observed after switching from one factor VIII product to another in previously treated patients with more than 100 exposure days who have a previous history of inhibitor development. Therefore, it is recommended to monitor all patients carefully for inhibitor occurrence following any product switch.
The clinical relevance of inhibitor development will depend on the titre of the inhibitor, with low titre inhibitors which are transiently present or remain consistently low titre posing less of a risk of insufficient clinical response than high titre inhibitors.

In general, all patients treated with coagulation factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII inhibitor presence should be performed. In patients with high levels of inhibitor, factor VIII therapy may not be effective and other therapeutic options should be considered. Management of such patients should be directed by physicians with experience in the care of haemophilia and factor VIII inhibitors.

Continuous infusion

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

Sodium content

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

Cardiovascular events

Haemophilic patients with cardiovascular risk factors or 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.

Development of neutralising antibodies (inhibitors) may occur in patients with haemophilia A treated with factor VIII, including with KOGENATE Bayer. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted.

Tabulated list of adverse reactions

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

Frequencies have been evaluated according to the following convention: very common: ($\geq 1/10$), common ($\geq 1/100$ to $<1/10$), uncommon ($\geq 1/1,000$ to $<1/100$), rare ($\geq 1/10,000$ to $<1/1,000$), very rare ($<1/10,000$), not known (cannot be estimated from the available data).
Table 3: Frequency of adverse drug reactions

<table>
<thead>
<tr>
<th>MedDRA Standard System Organ Class</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Very common</td>
</tr>
<tr>
<td>Blood and the Lymphatic System Disorders</td>
<td>FVIII Inhibition (PUPs)*</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>Infusion site reaction</td>
</tr>
<tr>
<td>Immune System Disorders</td>
<td>Skin associated hypersensitivity reactions, (pruritus, urticaria and rash)</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Dysgeusia</td>
</tr>
</tbody>
</table>

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

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

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

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Pharmacotherapeutic group: antihemorrhagics: blood coagulation factor VIII, ATC code B02BD02.
**Mechanism of action**

The factor VIII/von Willebrand factor (vWF) complex consists of two molecules (factor VIII and vWF) with different physiological functions. When infused into a haemophilic patient, factor VIII binds to vWF in the patient’s circulation. Activated factor VIII acts as a cofactor for activated factor IX, accelerating the conversion of factor X to activated factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed. Haemophilia A is a sex-linked hereditary disorder of blood coagulation due to decreased levels of factor VIII:C and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. By replacement therapy the plasma levels of factor VIII are increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

**Pharmacodynamic effects**

Determination of activated partial thromboplastin time (aPTT) is a conventional in vitro assay method for biological activity of factor VIII. The aPTT is prolonged in all haemophiliacs. The degree and duration of aPTT normalisation observed after administration of 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 system, 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 \textit{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 \textit{in vitro} studies.

Do not refrigerate after reconstitution.

\textbf{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.

\textbf{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 system, containing powder (10 mL clear glass type 1 vial with latex-free grey halogenobutyl rubber blend stopper plus transfer system with protective cap [Bio-Set])
- one pre-filled syringe with 2.5 mL (for 250 IU, 500 IU and 1000 IU) or 5 mL (for 2000 IU and 3000 IU) 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

\textbf{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.

The reconstituted medicinal product is a clear and colourless solution.

KOGENATE Bayer powder should only be reconstituted with the supplied solvent (2.5 mL (for 250 IU, 500 IU and 1000 IU) or 5 mL (for 2000 IU and 3000 IU) water for injections) in the prefilled syringe and the integrated transfer system (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 AG.

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

7. MARKETING AUTHORISATION HOLDER

Bayer AG
51368 Leverkusen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/143/004 - KOGENATE Bayer 250 IU
EU/1/00/143/005 - KOGENATE Bayer 500 IU
EU/1/00/143/006 - KOGENATE Bayer 1000 IU
EU/1/00/143/010 - KOGENATE Bayer 2000 IU
EU/1/00/143/012 - KOGENATE Bayer 3000 IU

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.
1. **NAME OF THE MEDICINAL PRODUCT**

KOGENATE Bayer 250 IU powder and solvent for solution for injection  
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KOGENATE Bayer 2000 IU powder and solvent for solution for injection  
KOGENATE Bayer 3000 IU powder and solvent for solution for injection

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**


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

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

The potency (IU) is determined using the one-stage clotting assay against the FDA Mega standard which was calibrated against WHO standard in International Units (IU).

The specific activity of KOGENATE Bayer is approximately 4000 IU/mg protein.

For the full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Powder and solvent for solution for injection (vial adapter).

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

4. **CLINICAL PARTICULARS**

4.1 **Therapeutic indications**

Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). This preparation does not contain von Willebrand factor and is therefore not indicated in von Willebrand's disease.
This product is indicated for adults, adolescents and children of all ages.

4.2 **Posology and method of administration**

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

**Posology**

The number of units of factor VIII administered is expressed in International Units (IU), which are related to the current WHO standard for factor VIII products. Factor VIII activity in plasma is expressed either as a percentage (relative to normal human plasma) or in International Units (relative to the International Standard for factor VIII in plasma).

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

**On demand treatment**

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

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

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

The dose, frequency and duration of the substitution therapy must be individualised according to the patient's needs (weight, severity of disorder of the haemostatic function, the site and extent of the bleeding, the presence of inhibitors, and the factor VIII level desired).
The following table provides a guide for factor VIII minimum blood levels. In the case of the haemorrhagic events listed, the factor VIII activity should not fall below the given level (in % of normal) in the corresponding period:

**Table 1: Guide for dosing in bleeding episodes and surgery**

<table>
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<tr>
<th>Degree of haemorrhage/Type of surgical procedure</th>
<th>Factor VIII level required (%) (IU/dl)</th>
<th>Frequency of doses (hours)/Duration of therapy (days)</th>
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<td><strong>Haemorrhage</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early haemarthrosis, muscle bleed or oral bleed</td>
<td>20 - 40</td>
<td>Repeat every 12 to 24 hours. At least 1 day, until the bleeding episode as indicated by pain is resolved or healing is achieved.</td>
</tr>
<tr>
<td>More extensive haemarthrosis, muscle bleed or haematoma</td>
<td>30 - 60</td>
<td>Repeat infusion every 12 - 24 hours for 3 - 4 days or more until pain and disability are resolved.</td>
</tr>
<tr>
<td>Life threatening haemorrhages (such as intracranial bleed, throat bleed, severe abdominal bleed)</td>
<td>60 - 100</td>
<td>Repeat infusion every 8 to 24 hours until threat is resolved</td>
</tr>
<tr>
<td><strong>Surgery</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Minor including tooth extraction</td>
<td>30 - 60</td>
<td>Every 24 hours, at least 1 day, until healing is achieved.</td>
</tr>
</tbody>
</table>
| Major (pre- and postoperative)                   | 80 - 100                              | 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.

\[
\text{Infusion rate (in IU/kg/h) = Clearance (in mL/h/kg) \times \text{desired factor VIII level (in IU/mL)}}
\]

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.

**Special populations**

**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 2 to 5 minutes. The rate of administration should be determined by the patient’s comfort level (maximal rate of infusion: 2 mL/min).

**Continuous infusion**

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).
Table 2: Example for calculation of infusion rate for continuous infusion after initial bolus injection

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

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

Cases of recurrent inhibitor (low titre) have been observed after switching from one factor VIII product to another in previously treated patients with more than 100 exposure days who have a previous history of inhibitor development. Therefore, it is recommended to monitor all patients carefully for inhibitor occurrence following any product switch.
The clinical relevance of inhibitor development will depend on the titre of the inhibitor, with low titre inhibitors which are transiently present or remain consistently low titre posing less of a risk of insufficient clinical response than high titre inhibitors.

In general, all patients treated with coagulation factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII inhibitor presence should be performed. In patients with high levels of inhibitor, factor VIII therapy may not be effective and other therapeutic options should be considered. Management of such patients should be directed by physicians with experience in the care of haemophilia and factor VIII inhibitors.

**Continuous infusion**

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

**Sodium content**

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

**Cardiovascular events**

Haemophilic patients with cardiovascular risk factors or 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.

Development of neutralising antibodies (inhibitors) may occur in patients with haemophilia A treated with factor VIII, including with KOGENATE Bayer. If such inhibitor occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted.

Tabulated list of adverse reactions

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

Frequencies have been evaluated according to the following convention: very common: (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).
### Table 3: Frequency of adverse drug reactions

<table>
<thead>
<tr>
<th>MedDRA Standard System Organ Class</th>
<th>Frequency Class</th>
<th>Frequency</th>
<th>Very Rare / not known</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood and the Lymphatic System Disorders</strong></td>
<td>Very common</td>
<td>FVIII Inhibition (PUPs)*</td>
<td>FVIII Inhibition (PTPs)*</td>
</tr>
<tr>
<td></td>
<td>Common</td>
<td>Infusion site reaction</td>
<td>Infusion related febrile reaction (pyrexia)</td>
</tr>
<tr>
<td></td>
<td>Uncommon</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Rare</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Very Rare / not known</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>General Disorders and Administration Site Conditions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Immune System Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Skin associated hypersensitivity reactions, (pruritus, urticaria and rash)</td>
<td>Systemic Hypersensitivity reactions (including anaphylactic reaction, nausea, blood pressure abnormal and, dizziness)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dysgeusia</td>
</tr>
<tr>
<td><strong>Nervous System Disorders</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

**Paediatric population**

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

**Reporting of suspected adverse reactions**

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

### 4.9 Overdose

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

### 5. PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

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

The factor VIII/von Willebrand factor (vWF) complex consists of two molecules (factor VIII and vWF) with different physiological functions. When infused into a haemophilic patient, factor VIII binds to vWF in the patient’s circulation. Activated factor VIII acts as a cofactor for activated factor IX, accelerating the conversion of factor X to activated factor X. Activated factor X converts prothrombin into thrombin. Thrombin then converts fibrinogen into fibrin and a clot can be formed. Haemophilia A is a sex-linked hereditary disorder of blood coagulation due to decreased levels of factor VIII:C and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. By replacement therapy the plasma levels of factor VIII are increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

Pharmacodynamic effects

Determination of activated partial thromboplastin time (aPTT) is a conventional in vitro assay method for biological activity of factor VIII. The aPTT is prolonged in all haemophiliacs. The degree and duration of aPTT normalisation observed after administration of 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 (for 250 IU, 500 IU and 1000 IU) or 5 mL (for 2000 IU and 3000 IU) 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.

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

Bayer AG
51368 Leverkusen
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/00/143/007 - KOGENATE Bayer 250 IU
EU/1/00/143/008 - KOGENATE Bayer 500 IU
EU/1/00/143/009 - KOGENATE Bayer 1000 IU
EU/1/00/143/011 - KOGENATE Bayer 2000 IU
EU/1/00/143/013 - KOGENATE Bayer 3000 IU

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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

10. DATE OF REVISION OF THE TEXT

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