

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.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

KOGENATE Bayer 250 IU - Recombinant coagulation Factor VIII, 250 IU/vial.
KOGENATE Bayer 500 IU – Recombinant coagulation Factor VIII, 500 IU/vial.
KOGENATE Bayer 1000 IU – Recombinant coagulation Factor VIII, 1000 IU/vial.
KOGENATE Bayer 2000 IU - Recombinant coagulation Factor VIII, 2000 IU/vial.

INN: octocog alfa.

Recombinant Coagulation Factor VIII is produced from genetically engineered baby hamster kidney cells containing the human factor VIII gene.

Solvent: water for injections.

KOGENATE Bayer 250 IU – The product reconstituted with the accompanying 2.5 ml of water for injections contains approximately 100 IU octocog alfa/ml.
KOGENATE Bayer 500 IU - The product reconstituted with the accompanying 2.5 ml of water for injections contains approximately 200 IU octocog alfa/ml.
KOGENATE Bayer 1000 IU - The product reconstituted with the accompanying 2.5 ml of water for injections contains approximately 400 IU octocog alfa/ml.
KOGENATE Bayer 2000 IU - The product reconstituted with the accompanying 5.0 ml of water for injections contains approximately 400 IU octocog alfa/ml.

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

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.

The powder is provided in a vial as a dry white to slightly yellow powder or cake.
The solvent is water for injections provided in a pre-filled syringe.

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.

4.2 Posology and method of administration

Treatment should be initiated 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. The calculation of the required dosage 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 dosage is determined using the following formulae:

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

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

The dosage 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 titre 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 bleeds such as intracranial bleed, throat bleed, severe abdominal bleed	60 - 100	Repeat infusion every 8 to 24 hours until threat is resolved
Surgery		
<i>Minor</i> including tooth extraction	30 - 60	Every 24 hours, at least 1 day, until healing is achieved.
<i>Major</i>	80 - 100 (pre- and postoperative)	a) By bolus infusions Repeat infusion every 8 - 24 hours until adequate wound healing occurs, then continue with therapy for at least another 7 days to maintain a factor VIII activity of 30% to 60% b) By continuous infusion Raise factor VIII activity pre-surgery with an initial bolus infusion and immediately follow with continuous infusion (in IU/Kg/h) adjusting according to patient's daily clearance and desired factor VIII levels for at least 7 days.

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, achieving different levels of *in vivo* recovery and demonstrating different half-lives.

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. 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) x 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.

For scheduled prophylaxis against bleeds in patients with severe haemophilia A, doses of 20 to 60 IU of KOGENATE Bayer per kg body weight should be given at intervals of 2 to 3 days. In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary. Data have been obtained in 61 children under 6 years of age.

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.

Administration

Reconstitute the preparation as described in 6.6.

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 injection: 2 ml/min).

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).

	Desired plasma FVIII level	Infusion rate IU/h/kg	Infusion rate for 75 kg patient ml/h		
			100 IU/ml	200 IU/ml	400 IU/ml
Clearance: 3 ml/h/kg			Concentrations of rFVIII solution		
	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.

Subsequent infusion rates should be calculated based on the actual FVIII levels and recalculated clearance for each day post surgery based on the equation:

clearance = infusion rate/actual FVIII level.

4.3 Contraindications

Known hypersensitivity to the active substance, to mouse or hamster protein or to any of the excipients.

4.4 Special warnings and precautions for use

As with any intravenous protein product, allergic type hypersensitivity reactions are possible. Patients should be made aware that the potential occurrence of chest tightness, dizziness, mild hypotension and nausea during infusion can constitute an early warning for hypersensitivity and anaphylactic reactions. Symptomatic treatment and therapy for hypersensitivity should be instituted as appropriate. If allergic or anaphylactic reactions occur, the injection/infusion should be stopped immediately and the patient should contact their physician. In case of shock, the current medical standards for shock treatment should be observed.

The formation of neutralising antibodies (inhibitors) to factor VIII is a known complication in the management of individuals with haemophilia A. These inhibitors are invariably IgG immunoglobulins directed against the factor VIII procoagulant activity, which are quantified in Modified Bethesda Units (BU) per ml of plasma. The risk of developing inhibitors is correlated to the exposure to anti-haemophilic 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 recombinant factor VIII product to another in previously treated patients with more than 100 exposure days who have a history of inhibitor development.

Patients treated with recombinant coagulation factor VIII should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. See also section 4.8 Undesirable effects.

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.

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

4.5 Interactions with other medicinal products and other forms of interaction

No interactions of KOGENATE Bayer with other medicinal products are known.

4.6 Pregnancy and lactation

Animal reproduction studies have not been conducted with KOGENATE Bayer.

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 lactation only if clearly indicated.

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

The frequencies of adverse drug reactions reported with KOGENATE Bayer are summarized in the table below. Within each frequency group, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$), and rare ($\geq 1/10,000$ to $< 1/1,000$).

Medical Entity (PTs)			
System Organ Class	*Common	*Uncommon	*Rare
Blood and the Lymphatic System Disorders	*Inhibitor Formation to FVIII (*Reported in PUP/MTP clinical trials)	**Inhibitor Formation to FVIII (**Reported in PTP and PMS)	
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 one anaphylactic reaction, nausea, blood pressure abnormal and, dizziness)

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

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

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

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

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

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 section 4.3 and 4.4).

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

The factor VIII/von Willebrand factor (vWF) complex consists of two molecules (factor VIII and vWF) with different physiological functions. When infused into a haemophiliac 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.

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.

5.2 Pharmacokinetic properties

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.

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 or solvents. 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 coagulation factor VIII adsorption to the internal surfaces of some infusion equipment.

6.3 Shelf-life

KOGENATE Bayer 250 IU, 500 IU, 1000 IU: 30 months.

KOGENATE Bayer 2000 IU: 24 months

After reconstitution, the product should be used immediately. However, chemical and physical in-use stability has been demonstrated for 48 hours at 30°C.

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.

The product when kept in its outer carton may be stored at ambient room temperature (up to 25°C) for a limited period of 3 months. In this case, the product expires at the end of this 3-month period; the new expiry date must be noted on the outer carton.

Do not refrigerate after reconstitution. For single use only. Any unused solution must be discarded.

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

6.5 Nature and contents of container

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 (250 IU, 500 IU, 1000 IU) or 5.0ml solvent (2000IU) (clear glass cylinder type 1 with latex-free grey bromobutyl rubber blend stopper)
- syringe plunger rod
- one venipuncture set
- two sterile 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 or 5.0ml water for injections) in the pre-filled syringe and the integrated transfer device (Bio-Set). Reconstitution should be performed in accordance with good practices rules, particularly with attention to asepsis. Gently rotate the vial until all powder is dissolved. After reconstitution the solution is clear. Do not use KOGENATE Bayer if you notice visible particulate matter or turbidity.

After reconstitution, the solution is drawn back into the syringe. Use the provided venipuncture set for intravenous injection.

Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Bayer Schering Pharma AG
13342 Berlin
Germany

8. MARKETING AUTHORISATION NUMBER(S)

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

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 04 August 2000
Date of last renewal: 04 August 2005

10. DATE OF REVISION OF THE TEXT

KOGENATE Bayer 250 IU – 04/2009
KOGENATE Bayer 500 IU – 04/2009
KOGENATE Bayer 1000 IU – 04/2009
KOGENATE Bayer 2000 IU – 04/2009

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

LEGAL CATEGORY

POM

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Bayer Schering Pharma