

SCHEDULING STATUS:

S4

PROPRIETARY NAMES AND DOSAGE FORM:

KOGENATE® FS 250, POWDER FOR INJECTION

KOGENATE® FS 500, POWDER FOR INJECTION

KOGENATE® FS 1000, POWDER FOR INJECTION

DILUENT FOR KOGENATE® FS: Sterile Water for Injection (SWI)

COMPOSITION:

**KOGENATE® FS 250 (Formulated with Sucrose):**

One vial of lyophilised powder contains 250 IU recombinant antihæmophilic Factor VIII (octocog alfa)

**KOGENATE® FS 500 (Formulated with Sucrose):**

One vial of lyophilised powder contains 500 IU recombinant antihæmophilic Factor VIII (octocog alfa)

**KOGENATE® FS 1000 (Formulated with Sucrose):**

One vial of lyophilised powder contains 1000 IU recombinant antihæmophilic Factor VIII (octocog alfa)

**The amount of sucrose in each vial is 28 mg and will not affect blood glucose levels.**

**DILUENT FOR KOGENATE® FS:** One prefilled syringe of Diluent for KOGENATE FS contains 2,5 ml Sterile Water for Injection.

PHARMACOLOGICAL CLASSIFICATION:

A 8.1 Coagulants, hæmostatics (ATC-Code B02B D02)

PHARMACOLOGICAL ACTION:

**Pharmacodynamic properties:**

The factor VIII/von Willebrand factor (vWF) complex consists of two molecules (factor VIII and vWF) with different physiological functions. When infused into a hæmophilic patient, factor VIII binds to vWF in the patient's circulation. Activated factor VIII acts as a co-factor 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.

Hæmophilia 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 (aPTT) is a conventional *in vitro* assay method for biological activity of factor VIII. The aPTT is prolonged in all hæmophiliacs. The degree and duration of aPTT normalisation observed after administration of KOGENATE FS is similar to that which is achieved with plasma-derived factor VIII.

KOGENATE FS Antihæmophilic Factor (Recombinant) is a sterile, stable, purified, nonpyrogenic, dried concentrate that has been manufactured using recombinant DNA technology. KOGENATE FS is intended for use in the treatment of bleeding in patients with classical hæmophilia (hæmophilia A). KOGENATE FS is produced by Baby Hamster Kidney (BHK) cells into which the human factor VIII (FVIII) gene has been introduced.

KOGENATE FS is a highly purified glycoprotein consisting of multiple peptides including an 80 kD and various extensions of the 90 kD subunit. It has the same biological activity as FVIII derived from human plasma. Compared to its predecessor product (KOGENATE manufactured with Human Albumin), KOGENATE FS incorporates a revised purification and formulation process that eliminates the addition of Albumin (Human).

**Pharmacokinetic properties:**

Factor VIII is immediately and completely bioavailable in the circulation after intravenous administration. Factor VIII activity decreased by a two-phase exponential decay with a clinically relevant terminal half-life of approximately 15 hours (range 11 – 20 hours). This behaviour is similar to that of plasma-derived Factor VIII with a mean terminal half-life of 13 hours (range 11-17 hours).

**INDICATIONS:**

Indicated in congenital Factor VIII deficiency (haemophilia A) for the treatment and prophylaxis of bleeding (in previously treated and untreated patients).

Indicated in patients with Factor VIII inhibitors (neutralizing antibodies) who continue to respond to KOGENATE FS (i.e. achievement of haemostasis) see "Dosage and direction for use".

**KOGENATE FS does not contain von Willebrand factor and hence is NOT indicated in von Willebrand's disease.**

**CONTRA-INDICATIONS:**

Hypersensitivity to any of the ingredients, including excipients. Known hypersensitivity to mouse or hamster protein.

**WARNINGS AND PRECAUTIONS:**

KOGENATE FS Antihaemophilic Factor (Recombinant) is intended for the treatment of bleeding disorders arising from a deficiency in FVIII. This deficiency should be proven prior to administering KOGENATE FS. The development of circulating neutralising antibodies to FVIII may occur during the treatment of patients with Haemophilia A. Inhibitor formation is especially common in young children with severe haemophilia during their first years of treatment, or in patients of any age who have received little previous treatment with FVIII. Nonetheless, inhibitor formation may occur at any time in the treatment of a patient with Haemophilia A. Patients treated with any anti-haemophilic factor preparation (AHF), including KOGENATE FS, should be carefully monitored for the development of antibodies to FVIII by appropriate clinical observation and laboratory tests, according to the recommendation of the patient's haemophilic treatment centre.

Patients should be made aware that the potential occurrence of chest tightness, dizziness, mild hypotension and nausea during infusion could 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 should be stopped immediately. In case of shock, the current medical standards for shock treatment should be observed.

**Formation of Antibodies to Mouse and Hamster Protein:**

Assays to detect seroconversion to mouse and hamster protein were conducted on all patients in clinical studies. No patient has developed specific antibodies to these proteins after commencing study, and no animal protein associated serious allergic reactions have been observed with KOGENATE FS infusions. Although no such reactions were observed, patients should be made aware of the possibility of a hypersensitivity reaction to mouse and/or hamster protein, and alerted to the early signs of such a reaction (e.g. hives, localised or generalised urticaria, wheezing and hypotension). Patients should be advised to discontinue use of the product and contact their physician/doctor if such symptoms occur.

**Carcinogenesis, Mutagenesis, and Impairment of Fertility:**

*In vitro* evaluation of the mutagenic potential of KOGENATE FS failed to demonstrate reverse mutation or chromosomal aberrations at doses substantially greater than the maximum expected clinical dose. *In vivo* evaluation of KOGENATE FS in animals using doses ranging between 10 and 40 times the expected clinical maximum also indicated that KOGENATE FS does not possess a mutagenic potential. Long-term investigations of carcinogenic potential in animals have not been performed.

**Paediatric Use:**

KOGENATE FS is appropriate for use in paediatric patients of all ages, including neonates, infants, children, and adolescents. Safety and efficacy studies have been performed in previously untreated and minimally treated paediatric patients (n=62).

**Geriatric Use:**

Clinical studies with KOGENATE FS did not include sufficient numbers of patients aged 65 and over to be able to determine whether they respond differently from younger patients. However, clinical experience with KOGENATE FS (manufactured with Human Albumin) and other AHF products has not identified differences between the elderly and younger patients. As with any patient receiving KOGENATE FS, dose selection for an elderly patient should be individualised.

**INTERACTIONS:**

No interactions of KOGENATE FS with other medicines are known.

Analgesics such as acetylsalicylic acid, phenylbutazone and indomethacin impair platelet function, increase the tendency to bleed and should therefore not be given to haemophilics.

**PREGNANCY AND LACTATION:**

Animal reproduction studies have not been conducted with KOGENATE FS. It is also not known whether KOGENATE FS can cause foetal harm when administered to a pregnant woman or affect reproduction capacity. It should be used during pregnancy and lactation only if clearly indicated.

**DOSAGE AND DIRECTIONS FOR USE:**

Each vial of KOGENATE FS has the rFVIII potency in international units stated on the label based on the one-stage assay methodology. The reconstituted product must be administered within 3 hours after reconstitution. It is recommended to use the administration set provided.

The dosage of KOGENATE FS required for haemostasis must be individualised according to the needs of the patient, the severity of the deficiency, the severity of the haemorrhage, the presence of inhibitors and the FVIII level desired.

The clinical effect of KOGENATE FS is the most important element in evaluating the effectiveness of treatment. It may be necessary to administer more KOGENATE FS than estimated in order to attain satisfactory clinical results. If the calculated dose fails to attain the expected FVIII levels, or if bleeding is not controlled after administration of the calculated dosage, the presence of a circulating inhibitor in the patient should be suspected. Its presence should be substantiated and the inhibitor level quantified by appropriate laboratory tests. When an inhibitor is present, the dosage requirement for KOGENATE FS could be extremely variable among different patients and the optimal treatment can be determined only by the clinical response.

**Calculation of Dosage:**

$$\text{Expected \% factor VIII increase} = \frac{\text{\# units administered} \times 2\%/IU/kg}{\text{body weight (kg)}}$$

$$\text{Example for a 70 kg adult: } \frac{1400 \text{ IU} \times 2\%/IU/kg}{70 \text{ kg}} = 40\%$$

$$\text{Dosage required (IU)} = \frac{\text{body weight (kg)} \times \text{desired \% FVIII increase}}{2\%/IU/kg}$$

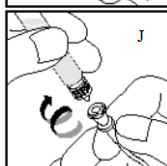
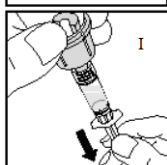
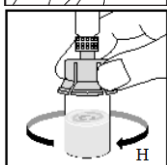
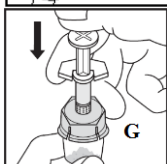
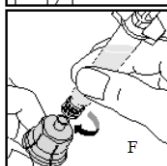
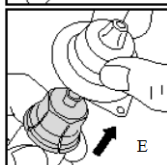
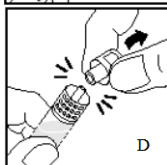
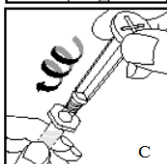
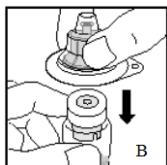
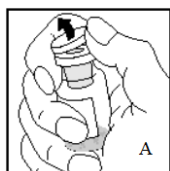
$$\text{Example for a 15 kg child: } \frac{15 \text{ kg} \times 100\%}{2\%/IU/kg} = 750 \text{ IU required}$$

The dosage necessary to achieve haemostasis depends upon the type and severity of the bleeding episode, according to the following general guidelines:

<b>Haemorrhagic event:</b>	<b>Therapeutically necessary plasma level of FVIII activity:</b>	<b>Dosage necessary to maintain the therapeutic plasma level:</b>
<b>Minor haemorrhage:</b> Superficial, early haemorrhage, haemorrhages into joints	20 – 40 %	10 – 20 IU per kg Repeat dose if evidence of further bleeding.
<b>Moderate to major haemorrhage:</b> Haemorrhages into muscles, oral cavity, definite haemarthroses, known trauma <b>Surgery:</b> minor surgical procedures	30 – 60 %	15 – 30 IU per kg Repeat one dose at 12 – 24 hours if needed.
<b>Major to life-threatening haemorrhage:</b> Intracranial, intraabdominal or intrathoracic haemorrhages, gastrointestinal bleeding, central nervous system bleeding, bleeding in the retropharyngeal or retroperitoneal spaces, or iliopsoas sheath <b>Fractures and Head trauma</b>	80 – 100 %	Initial dose 40 – 50 IU per kg Repeat dose 20 – 25 IU per kg every 8 – 12 hours
<b>Surgery:</b> Major surgical procedures	~ 100 %	Pre-operative dose 50 IU/kg Verify ~ 100 % activity prior to surgery. Repeat as necessary after 6 to 12 hours initially, and for 10 to 14 days until healing is complete.

**Instructions for use:**

Reconstitution, product administration and handling of the administration set and needles must be done with caution. Percutaneous puncture with a needle contaminated with blood can transmit infectious viruses including HIV (AIDS) and hepatitis. Obtain immediate medical attention if injury occurs.



## **MediMop Vial Adapter Instructions for use**

1. Wash 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). Aseptically cleanse the rubber stopper with alcohol, being careful not to handle the rubber stopper.
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. Carefully open the syringe blister pack by peeling the paper covering back to the midway point. Take out the pre-filled sterile water for injection (SWFI) syringe. Holding the plunger rod by the top plate, take it out of the blister pack. Avoid touching the sides and threads of the plunger rod. Hold the syringe upright, grasp the plunger rod by the top plate 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. Do not use solutions containing visible particles or that are cloudy.
11. Withdraw solution into the syringe by holding the vial on end above the vial adapter and syringe (I) then draw the plunger rod out slowly and smoothly. Ensure that the entire content of the vial is drawn into the syringe.
12. With the plunger rod in place, remove the syringe from the vial adapter (the latter should remain attached to the vial). Attach the syringe to the administration set provided and inject intravenously (J). NOTE: follow instructions for infusion set provided.
13. If the same patient is to receive more than one bottle, reconstitute each bottle with the diluent syringe provided then combine solutions in a larger syringe (not provided) and administer as usual.
14. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

**Rate of administration:**

The rate of administration should be adapted to the response of the individual patient, but administration of the entire dose in 5 to 10 minutes or less is well tolerated.

**SIDE EFFECTS AND SPECIAL PRECAUTIONS:**

System Organ Class	MedDRA
<b>Blood and lymphatic system disorders</b>	Factor VIII inhibition
<b>Gastrointestinal disorders</b>	Dysgeusia, Nausea
<b>General disorders and administrative site</b>	Injection site reaction
<b>Immune system disorders</b>	Allergic/Anaphylactic reaction
<b>Cardiovascular disorders</b>	Abnormal blood pressure
<b>Nervous system disorders</b>	Dizziness
<b>Skin and subcutaneous tissue disorders</b>	Pruritus, Rash

**KNOWN SYMPTOMS OF OVERDOSE AND PARTICULARS OF ITS TREATMENT:**

No information exists on symptoms of Factor VIII overdosage. Treatment is symptomatic and supportive.

**IDENTIFICATION:**

White to slightly yellow solid lyophilised powder (before reconstitution).  
Clear liquid after reconstitution with 2,5 ml Water for Injection.

**PRESENTATION:**

KOGENATE® FS 250, 500 or 1000:

White to slightly yellow solid lyophilised powder for solution for injection in 10 ml clear tubing glass vial with gray bromobutyl rubber stopper.

MEDIMOP®
1 vial of lyophilized product (Aluminium cap)
1 diluent prefilled syringe (Vetter)
1 Medimop vial adapter
BD-Infusion set

**STORAGE INSTRUCTIONS:**

Store in the refrigerator between 2°C to 8°C. Do not freeze. If stored at room temperature (up to 30 °C), the packed product may be kept for a limited period of 6 months.

Administer within 3 hours after reconstitution.

Protect from exposure to light and store the lyophilised powder in the carton prior to use.

KEEP OUT OF REACH OF CHILDREN.

**REGISTRATION NUMBERS:**

KOGENATE FS 250: 41/8.1/1086

KOGENATE FS 500: 41/8.1/1087

KOGENATE FS 1000: 41/8.1/1088

**NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:**

Bayer (Pty) Ltd  
27 Wrench Road  
Isando, 1609  
Registration number: 1968/11192/07

**DATE OF PUBLICATION OF THIS PACKAGE INSERT:**

10 October 2007

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