

## DATA SHEET

### KOGENATE® FS (with BIO-SET)

### octocog alfa (bhk) (recombinant Factor VIII)

#### NAME OF THE MEDICINE

KOGENATE FS 250 IU  
KOGENATE FS 500 IU  
KOGENATE FS 1000 IU  
KOGENATE FS 2000 IU  
KOGENATE FS 3000 IU

Octocog alfa (bhk) is a highly purified glycoprotein consisting of multiple peptides including an 80 kDa and various extensions of the 90 kDa subunit. KOGENATE FS is available in the following dose strengths:

**Table 1**

Available dose strengths and approximate concentration of reconstituted KOGENATE FS

KOGENATE FS dose strengths	Concentration of reconstituted KOGENATE FS
250 IU	~ 100 IU/mL
500 IU	~ 200 IU/mL
1000 IU	~ 400 IU/mL
2000 IU	~ 400 IU/mL
3000 IU	~ 600 IU/mL

Each vial of KOGENATE FS contains the labelled amount of octocog alfa (bhk) [Factor VIII] in International Units (IU). One IU, as defined by the World Health Organisation standard for blood coagulation Factor VIII, human, is approximately equal to the level of Factor VIII activity found in 1.0 mL of fresh pooled human plasma.

One single-use vial with lyophilisate for injection or infusion contains:

Active ingredient: octocog alfa (bhk) (nominal dose of 250, 500, 1000, 2000, or 3000 IU).

Excipients: sucrose, histidine, glycine, sodium chloride, calcium chloride and polysorbate 80.

[Trace amounts of mouse and hamster protein are also present.]

One single-use prefilled diluent syringe for parenteral use contains:

Excipient: water for injections, 2.5 mL for 250, 500, 1000 IU; 5 mL for 2000, 3000 IU.

#### PHARMACOLOGY

KOGENATE FS has the same biological activity as Factor VIII derived from human plasma with the exception that KOGENATE FS does not contain von Willebrand factor.

#### Pharmacodynamics

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 FS. This result is similar to the reported values for Factor VIII derived from human plasma.

Determination of activated partial thromboplastin time (aPTT) is a conventional *in vitro* assay method of biological activity of Factor VIII. The aPTT is prolonged in all haemophiliacs. The degree and

duration of aPTT normalisation observed after administration of KOGENATE FS is similar to that achieved with plasma-derived Factor VIII.

## **Pharmacokinetics**

### ***Absorption***

Not applicable. KOGENATE FS is administered directly into the blood stream by IV injection.

### ***Distribution***

No specific distribution studies have been performed, however, after administration of KOGENATE FS, peak Factor VIII activity decreases by a two-phase exponential decay. This is similar to that of plasma-derived Factor VIII. Factor VIII (rDNA) (bhk) binds to its natural protein carrier vWF and is mostly confined into the vascular space.

### ***Metabolism***

Factor VIII (rDNA) (bhk) is metabolised as it produces its biological activity during the activation of the coagulation cascade.

### ***Excretion***

After administration of KOGENATE FS, 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 approximately 13 hours. The half-life data for Factor VIII (rDNA) (bhk) were unchanged after 24 weeks of exclusive treatment, indicating continued efficacy and no evidence of Factor VIII inhibition.

## **INDICATIONS**

KOGENATE FS is indicated in congenital Factor VIII deficiency (haemophilia A) for the treatment and prophylaxis of bleeding in untreated and previously treated patients without inhibitors.

Routine prophylactic treatment to reduce the frequency of bleeding episodes and the risk of joint damage in children with no pre-existing joint damage.

Treatment can be continued in patients who develop Factor VIII inhibitors (neutralising antibodies, less than 10 Bethesda Units [BU]) and continue to respond to KOGENATE FS.

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

## **CONTRAINDICATIONS**

Known intolerance or allergic reactions to constituents of the preparation.

Known hypersensitivity to mouse or hamster protein may be a contraindication to the use of KOGENATE FS.

## WARNINGS AND PRECAUTIONS

### Hypersensitivity and anaphylactic reactions

KOGENATE FS contains trace amounts of mouse and hamster proteins. Caution should be exercised when administering to individuals with previous hypersensitivity to KOGENATE or plasma-derived Factor VIII, or known hypersensitivity to biological preparations with traces of murine or hamster proteins. Assays to detect seroconversion to mouse and hamster protein were conducted on all patients in the clinical trials. No patient developed specific antibodies to these proteins after commencing the study and no animal protein associated serious allergic reactions have been observed with KOGENATE FS infusions.

Although no such reactions have been observed to date, patients should be warned of the possibility of a hypersensitivity reaction to mouse and hamster protein, and alerted to the early signs of such a reaction (e.g. hives, generalised urticaria, wheezing and hypotension). Patients should be advised to discontinue use of the product and contact their physician if such symptoms occur.

Patients should be made aware that the occurrence of chest tightness, dizziness, mild hypotension, nausea and urticaria during infusion constitute an early warning for hypersensitivity and anaphylactic reactions. Very rare cases of allergic and anaphylactic reactions have been reported with the predecessor product, KOGENATE Factor VIII (rDNA) (bhk), particularly in very young patients or patients who had previously reacted to other Factor VIII concentrates (see **ADVERSE EFFECTS, Post-marketing experience**). Symptomatic treatment and therapy for hypersensitivity should be instituted as appropriate. Serious anaphylactic reactions require immediate emergency treatment with resuscitative measures such as the administration of adrenaline and oxygen. If allergic or anaphylactic reactions occur, the injection/infusion should be stopped immediately. In case of shock, the current medical standards for shock treatment should be observed.

### Monitoring

Although dosage can be estimated by the presented calculations, it is strongly recommended that laboratory tests be performed on the patient's plasma at suitable intervals to ensure that adequate Factor VIII levels have been reached and are maintained. In the case of major surgical interventions, a precise monitoring of the substitution therapy by means of coagulation analysis is required.

### Immunogenicity

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.

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 Factor VIII. Inhibitor formation may occur at any time during the treatment of patients with haemophilia A, therefore patients treated with any Factor VIII preparation, including KOGENATE FS, should be carefully monitored for the development of antibodies to Factor VIII by appropriate clinical observation and laboratory tests, according to the recommendation of the patient's haemophilia treatment centre (see **ADVERSE EFFECTS**).

If the Factor VIII level of the patient's plasma fails to reach expected levels, or if bleeding is not controlled after apparently adequate dosage, the presence of Factor VIII inhibitors should be suspected. The presence of Factor VIII inhibitors must be demonstrated and quantified by appropriate laboratory procedures (see **DOSAGE AND ADMINISTRATION**).

## **Catheter-related infections**

Catheter-related infections may be observed when KOGENATE FS is administered via central venous access devices (CVADs). These infections have not been associated with the product itself.

## **Pregnancy and lactation**

Animal reproduction studies have not been conducted with KOGENATE FS. Experience regarding the use of KOGENATE FS during pregnancy and lactation is not available due to the rare occurrence of haemophilia A in women. It is not known whether KOGENATE FS can cause foetal harm when administered to a pregnant woman or can affect reproductive capacity. It is not known if KOGENATE FS or its metabolites are excreted in human milk, and nursing is not recommended in women being treated with KOGENATE FS. KOGENATE FS should be used during pregnancy and lactation only if clearly indicated.

## **Preclinical safety data**

Doses several fold higher than the recommended clinical dose (related to body weight) did not demonstrate any acute or subacute toxic effects for octocog alfa 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 mammalian species.

*In vitro* evaluation of the mutagenic potential of first generation Factor VIII (rDNA) (bhk) did not demonstrate reverse mutation or chromosomal aberrations at doses substantially greater than the maximum expected clinical dose. *In vivo* evaluation of Factor VIII (rDNA) (bhk) 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.

## **Effect on ability to drive and use machines**

No effects on the ability to drive or to use machines have been observed.

## **INTERACTIONS WITH OTHER MEDICINES**

Besides the known interactions of Factor VIII with other coagulation proteins, no other interactions with other drugs have been established.

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

## ADVERSE EFFECTS

The adverse drug reactions are presented within each frequency grouping and system organ classes. Those in *italics* are post-marketing experience events.

**Table 2**

Adverse drug reactions and post-marketing experience for KOGENATE FS

Common (≥1% to <10%)	Uncommon (≥0.1% to <1%)	Rare (≥0.01% to <0.1%)	Very Rare / Unknown (<0.01%)
<b>Blood and the lymphatic system disorders</b>			
Inhibitor formation to Factor VIII (reported in PUPs/MTPs clinical trials)	<i>Inhibitor formation to Factor VIII (reported in PTPs and PMS)</i>		
<b>General disorders and administration site conditions</b>			
Infusion site reaction			<i>Infusion related febrile reaction</i>
<b>Immune system disorders</b>			
Skin associated hypersensitivity reactions			<i>Systemic hypersensitivity reactions (including one anaphylactic reaction)</i>
<b>Nervous system disorders</b>			
			<i>Dysgeusia</i>

PUPs = previously untreated patient, defined as having zero exposure days

MTPs = minimally treated patient, defined as having ≤ 4 exposure days

PTPs = previously treated patient, defined as having more than 100 exposure days

PMS = post marketing studies

During studies, no patient developed clinically relevant antibody titres against trace amounts of mouse and hamster protein present in the preparation, and no animal protein associated serious allergic reactions have been observed with KOGENATE FS infusions.

In clinical studies with 60 previously untreated patients (PUPs) and minimally treated paediatric patients (MTPs, defined as having equal to or less than 4 exposure days), 9 out of 60 (15%) PUPs/MTPs treated with KOGENATE FS 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). 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 (PTPs, defined as having more than 100 exposure days), followed over four years, de-novo inhibitors were not observed.

### Post-marketing experience

The following events are principally derived from post-marketing experience and publications, and accurate rate estimates are generally not possible. After administration of KOGENATE FS, in rare cases serious allergic / hypersensitivity reactions (which may include facial swelling, flushing, hives, blood pressure decrease, nausea, rash, restlessness, shortness of breath, tachycardia, tightness of the chest, tingling, urticaria, vomiting) have been reported, particularly in very young patients or patients who had previously reacted to other Factor VIII concentrates.

In extensive post-registration studies with KOGENATE FS, involving more than 1000 patients the following was observed: In the PUPs/MTPs (defined as having less than 20 exposure days) subset, less than 11% developed de-novo inhibitors. Less than 0.2% PTPs developed de-novo inhibitors.

## DOSAGE AND ADMINISTRATION

The dosage and duration of the substitution therapy to achieve haemostasis 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 clinical effect of Factor VIII 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 Factor VIII 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 quantitated by appropriate laboratory test. When an inhibitor is present, the dosage requirement for KOGENATE FS is extremely variable and the dosage can be determined only by the clinical response (see **WARNINGS AND PRECAUTIONS**).

Clinical studies have demonstrated a mean rise of about 2% in Factor VIII activity for each unit of KOGENATE FS administered per kg body weight. The following formulae may be used to determine the appropriate dose required for a given response (1) or the response to be expected from a given dose (2).

1. Required IU = body weight (kg) x desired Factor VIII rise (% of normal) x 0.5 (IU/kg)

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

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 3**

Dosage necessary to achieve haemostasis

<b>Haemorrhagic event</b>	<b>Therapeutically necessary plasma level of Factor VIII activity</b>	<b>Dosage and duration necessary to maintain the therapeutic plasma level</b>
<b>Minor haemorrhage</b> (superficial, early haemorrhages, haemorrhages into joints)	20-40%	10-20 IU per kg for at least 1 day. Repeat dose if evidence of further bleeding.
<b>Moderate to major haemorrhage</b> (haemorrhages into muscles, haemorrhages into the oral cavity, definite haemarthroses, known trauma)	30-60%	15-30 IU per kg. Repeat dose at 12-24 hours if needed for 3-4 days or until adequate wound healing.
<b>Surgery</b> (minor surgical procedures)		
<b>Major to life-threatening haemorrhage</b> (intra-cranial, intra-abdominal or intra-thoracic haemorrhages, gastrointestinal bleeding, central nervous system bleeding, bleeding in the retro pharyngeal or retro peritoneal spaces or iliopsoas sheath)	80-100%	Initial dose 40-50 IU per kg. Repeat dose 20-25 IU per kg every 8-12 hours for 7 days, then therapy for another 7 days to maintain Factor VIII level at 30-50%.
<b>Fractures</b>		
<b>Head trauma</b>		
<b>Surgery</b> (major surgical procedures)	~100%	By bolus infusions. Preoperative dose 50 IU per kg, verify ~100% activity prior to surgery. Repeat as necessary after 6-12 hours initially and for 10-14 days until healing is complete.

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 can be required, especially in the case of the initial dose.

KOGENATE FS may also be administered for prophylaxis (short or long term) of bleeding, as determined by the physician on an individual basis. However, doses of 10 to 50 IU of KOGENATE FS per kg body weight administered at intervals of 2 to 3 days have been successful in limiting the number of recurrent and problematic bleeding episodes. In some cases, especially younger patients, shorter dosage intervals or higher doses may be necessary.

### **Reconstitution and administration**

CONTAINS NO ANTIMICROBIAL AGENT. PRODUCT IS FOR SINGLE-USE IN ONE PATIENT ONLY.

### **General instructions**

KOGENATE FS is intended for intravenous administration only. To reduce microbiological hazard, it should be administered as soon as practicable and within 3 hours after reconstitution. If storage is

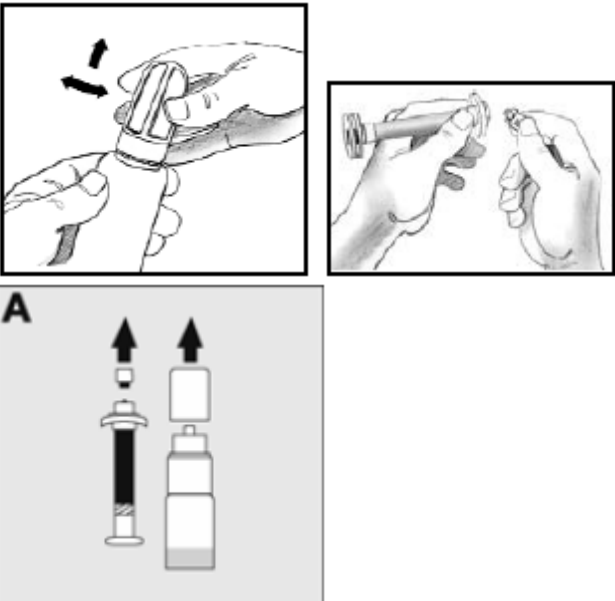
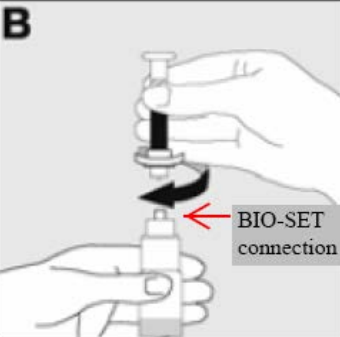
necessary hold at room temperature for not more than 3 hours. If the solution is not injected immediately after reconstitution, leave the syringe attached to the vial containing the solution to maintain sterility of the product. Refrigeration of reconstituted KOGENATE FS solution should be avoided. Any unused solution must be discarded.

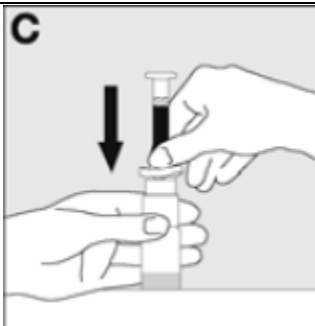
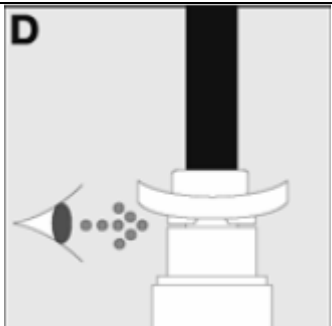
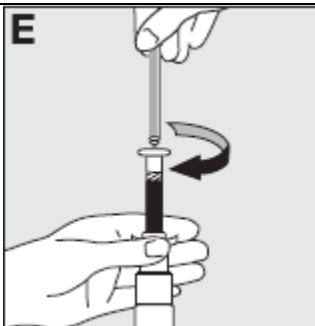
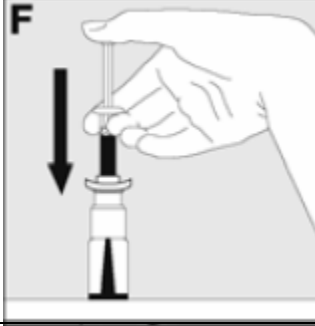
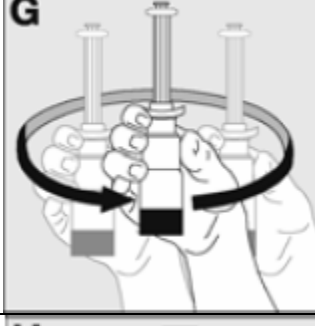
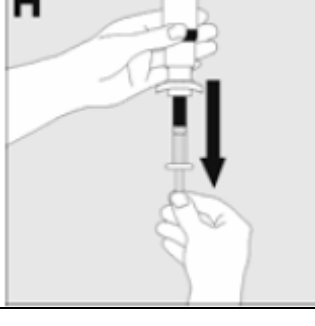
Data from clinical trials, including patients between 0-68 years old, shows that the entire dose is administered in a median of 5 minutes. The rate of administration should be adapted to the response of each individual patient.

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 and hepatitis. Obtain immediate medical attention if injury occurs. Place needles in a sharps container after single-use. Discard all equipment, including any reconstituted KOGENATE FS product, in accordance with biohazard procedures.

**Reconstitution**

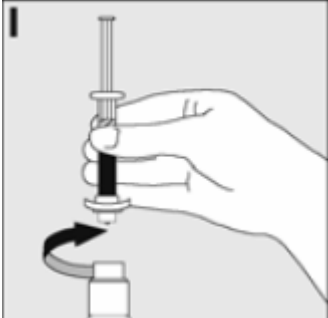

Wash your hands thoroughly before performing the following procedures. Prepare the solution on a clean, dry, non-slip surface.

<p>1. Warm the unopened powder vial and the diluent syringe in your hands to approximately body temperature (do not exceed 37°C).</p>	
<p>2. Remove the cap from the powder vial by gently rocking it from side to side several times, whilst at the same time pulling upwards. Remove the stopper attached to the white cap from the syringe (Figure A).</p>	
<p>3. Connect the diluent syringe to the powder vial by gently screwing the syringe on to the BIO-SET connection of the powder vial (Figure B).</p>	

<p>4. Place the vial on a clean, dry, non-slip surface and hold it firmly with one hand. With the other hand, strongly press down on the fingerplate near the syringe tip using your thumb and index finger (Figure C) until the fingerplate meets the top edge of the BIO-SET. A “click” will be heard. This indicates that the system is activated. (Figure D).</p>		
<p>5. Insert the plunger rod into the syringe barrel and screw it into the rubber stopper (Figure E).</p>		
<p>6. Inject the diluent into the powder by slowly pushing down on the syringe plunger rod (Figure F).</p>		
<p>7. Dissolve the powder by gently swirling the vial (Figure G). Do not shake the vial. Ensure that the powder is completely dissolved without excessive foam before use. Do not use solutions that contain visible particles or that are cloudy or discoloured.</p>		
<p>8. Invert vial/syringe and transfer the solution into the syringe by drawing the plunger out slowly and smoothly (Figure H). Ensure that the entire contents of the reconstituted KOGENATE FS vial are drawn into the syringe.</p>		
<p>9. If the same patient is to receive more than one dose, reconstitute the desired amount of product repeating steps 1-8 above. Use a new syringe.</p>		

## Administration

Wear gloves to avoid contact with blood.

<p>1. Apply a tourniquet. Determine the point of injection. Prepare the site of injection aseptically by cleaning the skin with an alcohol swab and letting it dry. Firmly grasp one or both wings of the administration set to puncture the vein and secure the administration set. NOTE: Follow instructions for administration set provided.</p>	
<p>2. Remove the tourniquet.</p>	
<p>3. Unscrew the filled syringe to disconnect from the empty vial (Figure I).</p>	
<p>4. Attach the filled syringe to the administration set by screwing it clockwise and ensure that no blood enters the syringe (Figure J).</p>	
<p>5. Inject the solution slowly over several minutes (from 1-2 mL per minute), keeping an eye on the position of the needle. The rate of administration should be adapted to the response of the individual patient, but administration of the entire dose in 5-10 minutes or less is well tolerated.</p>	
<p>6. If a further dose is required, remove the empty syringe by turning it anti-clockwise. Connect the newly prepared syringe. Follow steps 4-5 above.</p>	
<p>7. If no further dose is required, remove the administration set and syringe. Hold a swab firmly over the injection site on the outstretched arm for approximately 2 minutes. Finally, apply a small pressure dressing to the wound.</p>	

## Special populations

### Paediatrics (<18 years of age)

KOGENATE FS is appropriate for use in paediatric patients of all ages. Safety and efficacy studies have been performed in both previously untreated and minimally treated paediatric patients.

## **Geriatrics (>65 years of age)**

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 and other Factor VIII products has not identified differences between the elderly and younger patients. As with any patient receiving Factor VIII, dose selection for an elderly patient should be individualised.

## **Patients with inhibitors**

KOGENATE FS remains efficacious in patients who develop Factor VIII inhibitors (neutralising antibodies, less than 10 BU) during treatment. Factor VIII levels and inhibitor titres must be assessed to ensure adequate replacement therapy.

Patients with higher titre inhibitors may require an extensive Factor VIII concentrate infusion therapy. If haemostasis cannot be achieved with Factor VIII concentrate in the presence of high-titre inhibitors, the use of Factor VIIa concentrate or (activated) prothrombin complex concentrate (PCC) must be considered. These therapies should be directed by physicians with experience in the care of patients with haemophilia A.

## **OVERDOSAGE**

No information exists on symptoms of Factor VIII overdose.

## **PRESENTATION**

KOGENATE FS supplied with BIO-SET needleless reconstitution set is a self contained system provided with a prefilled syringe containing diluent for reconstitution.

KOGENATE FS 250 IU, 500 IU, 1000 IU

Packs of 1 vial of lyophilisate [250 IU, 500 IU, 1000 IU octocog alfa (bhk)] and a prefilled diluent syringe for reconstitution (2.5 mL Water for Injections).

KOGENATE FS 2000 IU, 3000 IU

Packs of 1 vial of lyophilisate [2000 IU, 3000 IU octocog alfa (bhk)] and a prefilled diluent syringe for reconstitution (5 mL Water for Injections).

Each pack of KOGENATE FS also contains:

- One sterile administration set
- One plunger rod
- Two alcohol swabs
- One cotton pad
- One bandage

Not all presentations are marketed.

## **PHARMACEUTICAL PRECAUTIONS**

### **Shelf-life and storage conditions**

KOGENATE FS must be used before the expiry date.

Protect KOGENATE FS from light. Keep KOGENATE FS in its carton until just prior to use.

The shelf life of KOGENATE FS 250 IU, 500 IU, 1000 IU, 2000 IU powder for injection is 30 months when stored at +2°C to +8°C, including storage at or below 25°C for a single period of 3 months.

The shelf life of KOGENATE FS 3000 IU powder for injection is 30 months when stored at +2°C to +8°C. Storage of KOGENATE FS 3000 IU may include storage at or below 30°C for a single period of 6 months.

The shelf life of the prefilled diluent syringe supplied with KOGENATE FS is 48 months at 2°C to 25°C, including storage at or below 30°C for a single period of 6 months.

KOGENATE FS should be stored under refrigeration. Do not freeze as the lyophilized powder glass vial and the diluent prefilled glass syringe may break.

Do not return the product to refrigeration after storage below 25°C or 30°C. Unused product must then be discarded.

### **Incompatibilities**

KOGENATE FS should not be mixed with other medicinal products or infusion solutions, as this could change the blood clotting activity. Use only the administration set provided. Treatment failure can occur as a consequence of human coagulation Factor VIII adsorption to the internal surfaces of some infusion equipment.

### **FURTHER INFORMATION**

#### **List of excipients**

250, 500, 1000 IU: One vial with lyophilised powder contains 58 mg glycine, 4.4 mg sodium chloride, 0.7 mg calcium chloride, 8 mg histidine, 200 µg polysorbate 80 and 28 mg sucrose.

2000, 3000 IU: One vial with lyophilised powder contains 110 mg glycine, 8.6 mg sodium chloride, 1.3 mg calcium chloride, 15.2 mg histidine, 400 µg polysorbate 80 and 52 mg sucrose.

### **MEDICINE CLASSIFICATION**

General sales medicine

### **NAME AND ADDRESS**

Bayer New Zealand Limited  
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North Shore, Auckland 0627  
New Zealand

### **DATE OF PREPARATION**

25 November 2011

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