KOGENATE® Bayer 250, 500, 1000, 2000 and 3000 IU powder and solvent for solution for injection (Octocog alfa) Prescribing Information
(Refer to full Summary of Product Characteristics (SmPC) before prescribing)

Presentation: Powder & solvent for solution for injection containing octocog alfa, human coagulation factor VIII (rDNA) (bhk). Reconstitute product with accompanying 2.5 mL (250, 500, 1000 IU) or 5.0 mL (2000, 3000 IU) water for injections; 250 IU gives approx. 100 IU octocog alfa/mL; 500 IU gives approx. 200 IU octocog alfa/mL; 1000 IU and 2000IU give approx. 400 IU octocog alfa/mL; 3000IU gives approx. 600 IU octocog alfa/mL. **Indication(s):** Treatment & prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). Indicated for adults, adolescents and children of all ages. This preparation does not contain von Willebrand factor and is therefore not indicated in von Willebrand's disease. **Posology and method of administration:** Calculation of required factor VIII (FVIII) dose is based on empirical finding that 1 IU FVIII per kg body weight raises plasma FVIII activity by 1.5–2.5% of normal activity. Required dosage is determined using following formulae:
I. Required IU = body weight (kg) x desired FVIII rise (% of normal) x 0.5
II. Expected FVIII rise (% of normal) = [2 x administered IU]/[body weight (kg)].
Dose, frequency and duration of substitution therapy must be based on patient's needs. The following provides a guide for FVIII minimum blood levels. ***Haemorrhage:*** *Early haemarthrosis, muscle bleed or oral bleed* – FVIII level required is 20– 40% (IU/dl) every 12–24 hrs for at least 1 day until bleeding episode as indicated by pain is resolved or healing achieved. *More extensive haemarthrosis, muscle bleed or haematoma* – FVIII level required is 30–60% (IU/dl) every 12–24 hrs for 3–4 days or more until pain and disability are resolved. *Life threatening haemorrhages such as intracranial bleed, throat bleed, severe abdominal bleed* – FVIII level required is 60 –100% (IU/dl) every 8–24 hrs until threat is resolved. ***Surgery****: Minor including tooth extraction* – FVIII level required is 30–60% (IU/dl) every 24 hrs for at least 1 day until healing is achieved. *Major* – FVIII level required is 80–100% (IU/dl) (pre- and post-operative) a) by Bolus Infusion: every 8–24 hrs until adequate wound healing, then therapy for at least another 7 days to maintain FVIII activity of 30–60% (IU/dl), b) by Continuous Infusion: raise FVIII activity pre-surgery with initial bolus infusion and immediately follow with continuous infusion (in IU/kg/h) adjusting according to patient's daily clearance and desired FVIII levels for at least 7 days. Dose & frequency of administration should be adapted to clinical effectiveness in individual case, in certain circumstances larger amounts may be required, especially of initial dose. ***Continuous infusion***: clinical and *in vitro* stability has been demonstrated using ambulatory pumps with PVC reservoir. KOGENATE Bayer contains low level of polysorbate-80 as an excipient, which is known to increase the rate of DEHP extraction from PVC materials. ***Prophylaxis:*** doses of 20–40 IU per kg body weight at intervals of 2–3 days in severe haemophilia A. In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary. ***Paediatric population:*** Safety and efficacy in children of all ages have been established. Data obtained from clinical trials in 61 children <6yrs of age and non-interventional studies in children of all ages. ***Patients with inhibitors:*** Patients with haemophilia A may develop neutralising antibodies (inhibitors) to FVIII. The condition may manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted. If inhibitors present at levels <10 BU/ml then administration of additional FVIII may neutralise inhibitor and permit continued clinically effective therapy. In presence of inhibitor, doses required are variable & must be adjusted according to clinical response & plasma FVIII activity. In patients with titres >10 BU or high anamnestic response, use of (activated) prothrombin complex concentrate (PCC) or recombinant activated FVII (rFVIIa) should be considered. These therapies should be directed by physicians with experience in the care of patients with haemophilia. ***Reconstitution and administration:*** Detailed instructions for preparation & administration are contained in the package leaflet. KOGENATE Bayer should be injected intravenously over 2 to 5 minutes. The rate of administration should be determined by the patient's comfort level (max. rate of infusion: 2 mL/min). KOGENATE Bayer can be infused by continuous infusion. The infusion rate should be calculated based on the clearance and desired FVIII level. During continuous infusion, infusion bags should be changed every 24 hours. **Contraindications:** Hypersensitivity to active substance, mouse/hamster protein or any of the excipients. **Warnings and precautions:** Allergic type hypersensitivity and anaphylactic reactions. Formation of neutralising antibodies (inhibitors). The product contains traces of mouse and hamster proteins and human proteins other than factor VIII. Cases of recurrence of inhibitors (low titre) have been observed after switching from one FVIII product to another in previously treated patients (PTPs) with more than 100 exposure days who have a history of inhibitor development. It is recommended to monitor all patients carefully for inhibitor occurrence following any product switch. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for the presence of factor VIII inhibitor should be performed. In patients with high levels of inhibitor, factor VIII therapy may not be effective and other therapeutic options should be considered. Management of such patients

should be directed by physicians with experience in the care of haemophilia and factor VIII inhibitors. In a clinical study about the use of continuous infusion in surgeries, heparin was used to prevent thrombophlebitis at infusion site as with any other long term intravenous infusions. Contains <1 mmol sodium (23 mg) per vial, i.e. essentially "sodium free". 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 at least 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. If central venous access device (CVAD) required, consider risk of CVAD-related complications including local infections, bacteremia and catheter site thrombosis. **Interactions:** None known. **Pregnancy and lactation:** No information – use only if clearly indicated. **Undesirable effects:** *Very common:* Inhibitor formation to FVIII (reported in previously untreated patients (PUPs) and minimally treated patients (MTPs), *Common:* infusion site reaction, skin associated hypersensitivity reactions (pruritus, urticaria & rash), *Serious: cf. CI/W&P - in addition:* Systemic hypersensitivity reactions reported rarely (including anaphylactic reaction, nausea, abnormal blood pressure & dizziness) which may in some cases progress to severe anaphylaxis (including shock). Inhibitor formation to FVIII reported uncommonly in previously treated patients (PTPs); In clinical studies, 14% PUPs and 17% minimally treated paediatric patients developed inhibitors within 20 exposure days. Overall, 9 out of 60 (15%) developed inhibitors. In clinical studies with 73 PTPs, followed over 4 years, no de-novo inhibitors were observed. In one observational study, the incidence of inhibitor development in PUPs with severe haemophilia A was 64/183 (37.7%) with KOGENATE Bayer (followed up to 75 exposure days). In extensive post-registration observational studies, involving >1000 patients, <0.2% PTPs developed de-novo inhibitors. Prescribers should consult the SmPC in relation to other side effects. 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. **Overdose:** No cases reported **Incompatibilities:** Must not be mixed with other medicinal products or solvents except those mentioned in SmPC. Only the provided components (powder vial, pre-filled syringe containing solvent, vial adapter & venipuncture set) should be used for reconstitution and injection because treatment failure can occur as a consequence of human recombinant coagulation FVIII adsorption to internal surfaces of some infusion equipment. **Special Precautions for Storage:** Store in a refrigerator (2^{o}C-8^{o}C). Do not freeze. Keep vial & pre-filled syringe in outer carton in order to protect from light. Within overall shelf-life of 30 months, product (in outer carton) may be stored at ambient room temp (up to 25^{o}C) for 12 months & expires at the end of this 12-month period or expiration date on vial, whichever is earlier. After reconstitution, from microbiological point of view, use immediately. Do not refrigerate after reconstitution. For single use only. Any unused solution must be discarded. **Legal Category:** POM. **Package Quantities and Basic NHS Costs:** Single dose vials containing 250 IU, 500 IU, 1000 IU, 2000 IU or 3000 IU octocog alfa powder, 2.5 mL or 5.0 mL water for injections syringe and administration set. 250 IU £157.50, 500 IU £315, 1000 IU £630, 2000 IU £1260, 3000 IU £1890 **MA Number(s):** EU/1/00/143/007-009, 011, 013. **Further information available from:** Bayer plc, Bayer House, Strawberry Hill, Newbury, Berkshire RG14 1JA United Kingdom. Telephone: 01635 563000. **Date of preparation:** September 2016

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard. Adverse events should also be reported to Bayer plc. Tel.: 01635 563500, Fax.: 01635 563703, Email: pvuk@bayer.com