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AFSTYLA®
Recombinant Blood Clotting Factor VIII, Lonoctocog Alfa

References

1. CSL Behring (05/2019). SPC Afstyla.
2. Mahlangu, J., et al. (2016). "Efficacy and safety of rVIII-SingleChain: results of a phase 1/3 multicenter clinical trial in severe hemophilia A." Blood 128(5): 630-637.
3. Stasyshyn, O., et al. (2017). "Safety, efficacy and pharmacokinetics of rVIII-SingleChain in children with severe hemophilia A: results of a multicenter clinical trial." J Thromb Haemost 15(4): 636-644.
4. Olivieri M, Sommerer P, Maro G, Yan S. Assessing prophylactic use and clinical outcomes in hemophilia A patients treated with rVIII-SingleChain and other common rFVIII products in Germany. Eur J Haematol. 2020;00:1-8. https://doi.org/10.1111/ejh.13378

Afstyla, powder and solvent for solution for injection

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions. **Name of the medicinal product and pharmaceutical form:** Afstyla 250 IU/ 500 IU/ 1000 IU/ 1500 IU/ 2000 IU/ 2500 IU/ 3000 IU, powder and solvent for solution for injection. White or slightly yellow powder or friable mass and clear, colourless solvent for solution for injection. pH: 6,6-7,3. Osmolalitity: 500-600 mOsm/kg. **Qualitative and quantitative composition:** Each vial contains nominally 250 IU/ 500 IU/ 1000 IU/ 1500 IU/ 2000 IU/ 2500 IU/ 3000 IU recombinant, single-chain coagulation factor (rVIII-SingleChain, INN = lonoctocog alfa). One ml Afstyla 250 IU/ 500 IU/ 1000 IU/ 1500 IU/ 2000 IU/ 2500 IU/ 3000 IU contains respectively 100 IU (250 IU/2,5ml) / 200 IU (500 IU/2,5ml) / 400 IU (1000 IU/2,5ml) / 300 IU (1500 IU/5ml) / 400 IU (2000 IU/5ml) / 500 IU (2500 IU/5ml) / 600 IU (3000 IU/5ml) rVIII-SingleChain, after reconstitution with water for injection. The potency (IU) is determined using the European Pharmacopoeia chromogenic assay. The specific activity of AFSTYLA is 7400 - 16000 IU/mg protein. AFSTYLA is a single-chain recombinant human factor VIII produced in Chinese hamster ovary (CHO) cells. It is a construct where most of the B-domain occurring in wild-type, full-length factor VIII and 4 amino acids of the adjacent acidic a3 domain were removed (amino acids 765 to 1652 of full-length factor VIII). The newly formed linkage of the heavy and light chain of factor VIII introduces a new N-glycosylation site. As the furin cleavage site present in wild type factor VIII between the B-domain and the a3 domain was removed, AFSTYLA is expressed as a single-chain factor VIII molecule. Afstyla 250 IU/ 500 IU en 1000 IU contains 17,5 mg (0,76 mmol) of sodium and Afstyla 1500 IU/ 2000 IU/ 2500 IU and 3000 IU contains 35 mg (1,52 mmol) of sodium. For the full list of excipients, see summary of product characteristics. **Therapeutic indications:** Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). AFSTYLA can be used for all age groups. **Posology:** Treatment should be under the supervision of a physician experienced in the treatment of haemophilia. Treatment monitoring: During the course of treatment, appropriate determination of factor VIII levels is advised to guide the dose to be administered and the frequency of repeated injections. Individual patients may vary in their responses to factor VIII, demonstrating different half-lives and recoveries. Dose based on bodyweight may require adjustment in underweight or overweight patients. 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. When using an in vitro thromboplastin time (aPTT)-based one stage clotting assay for determining factor VIII activity in patients' blood samples, plasma factor VIII activity results can be significantly affected by both the type of aPTT reagent and the reference standard used in the assay. Also there can be significant discrepancies between assay results obtained by aPTT-based one stage clotting assay and the chromogenic assay according to Ph. Eur. This is of importance particularly when changing the laboratory and/or reagents used in the assay. Plasma factor VIII activity in patients receiving AFSTYLA using either the chromogenic assay or the one-stage clotting assay should be monitored to guide the dose administered and the frequency of repeat injections. The chromogenic assay result most accurately reflects the clinical hemostatic potential of AFSTYLA and is preferred. The one-stage clotting assay result underestimates the factor VIII activity level compared to the chromogenic assay result by approximately 45%. If the one-stage clotting assay is used, multiply the result by a conversion factor of 2 to determine the patient's factor VIII activity level. Posology: The dose and duration of the substitution therapy depend on the severity of the factor VIII deficiency, on the location and extent of the bleeding and on the patient's clinical condition. The number of units of factor VIII administered is expressed in International Units (IU), which are related to the current WHO concentrate standard for factor VIII products. Factor VIII activity in plasma is expressed either as a percentage (relative to normal human plasma) or preferably in International Units (relative to an 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. Potency assignment is determined using a chromogenic substrate assay. Plasma factor VIII levels can be monitored using either a chromogenic substrate assay or a one-stage clotting assay. 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 2 IU/dl. The required dose is determined using the following formula: Dose (IU) = body weight (kg) x Desired factor VIII rise (IU/dl or % of normal) x 0.5 (IU/kg per IU/dl). The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case. In the case of the following haemorrhagic events, the factor VIII activity should not fall below the given plasma activity level (in % of normal or IU/dl) within the corresponding period. The following table can be used to guide dosing in bleeding episodes and surgery:

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 bleeding or oral bleeding	20 - 40	Repeat injection 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 bleeding or haematoma	30 - 60	Repeat injection every 12 to 24 hours for 3-4 days or more until pain and acute disability are resolved.
Life threatening haemorrhages	60 - 100	Repeat injection every 8 to 24 hours until threat is resolved.
Surgery		
Minor surgery including tooth extraction	30 - 60	Inject every 24 hours, at least 1 day, until healing is achieved.
Major surgery	80 - 100 (pre- and postoperative)	Repeat injection every 8 to 24 hours until adequate wound healing, then therapy for at least another 7 days to maintain a factor VIII activity of 30% to 60% (IU/dl).

Profylaxis: The recommended starting regimen is 20 to 50 IU/kg of AFSTYLA administered 2 to 3 times weekly. The regimen may be adjusted based on patient response. *Paediatric population*: The recommended starting regimen in children (0 to <12 years of age) is 30 to 50 IU per kg of AFSTYLA administered 2 to 3 times weekly. More frequent or higher doses may be required in children <12 years of age to account for the higher clearance in this age group. For adolescents of 12 years of age and above, the dose recommendations are the same as for adults (please refer to summary of product characteristics). *Elderly*: Clinical studies of AFSTYLA did not include subjects over 65 years of age. **Method of administration:** Intravenous use. For instructions on reconstitution of the medicinal product before administration, see summary of product characteristics.The reconstituted preparation should be injected slowly at a rate comfortable for the patient at a maximum injection rate of 10 ml/min. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients listed in the summary of product characteristics. Known allergic reaction to hamster proteins. **Undesirable effects:** Summary of the safety profile: Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the injection site, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) have been observed rarely with the use of factor VIII products and may in some cases progress to severe anaphylaxis (including shock). Development of neutralizing antibodies (inhibitors) may occur in patients with haemophilia A treated with factor VIII, including with AFSTYLA. If such inhibitors occur, the condition may manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted. List of adverse reactions: The data presented below is according to the MedDRA system organ classification (SOC and Preferred Term Level). The frequencies were observed in completed clinical studies in previously treated patients with severe haemophilia A. Frequencies have been evaluated on a per patient basis 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). *Blood and lymphatic system disorders*: uncommon (PTPs) – very common (PUPs): FVIII inhibitor (frequency is based on studies with all FVIII products which included patients with severe haemophilia A) ; *Immune system disorders*: common: hypersensitivity ; *Nervous system disorders*: common: dizziness, paraesthesia ; *Skin- and subcutaneous tissue disorders*: common: rash ; uncommon: erythema, pruritus ; *General disorders and administration site conditions*: common: pyrexia ; uncommon: injection site pain, chills, feeling hot. Paediatric population: No age-specific differences in adverse reactions were observed between paediatric and adult subjects. Reporting of suspected adverse reactions: Reporting suspected adverse reactions after authorization 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 Federal agency for medicines and health products - Department Vigilance - EUROSTATION II - Victor Hortaplein, 40/40 - B-1060 Brussels - Website: www.fagg.be e-mail: adversedrugreactions@fagg-afmps.be. **Marketing Authorisation Holder:** CSL Behring GmbH, Emil-von-Behring Straße 76, D-35041 Marburg, Duitsland; Afstyla 250 IU - EU/1/16/1158/001 / Afstyla 500 IU - EU/1/16/1158/002 / Afstyla 1000 IU - EU/1/16/1158/003 / Afstyla 1500 IU - EU/1/16/1158/004 / Afstyla 2000 IU - EU/1/16/1158/005 / Afstyla 2500 IU - EU/1/16/1158/006 / Afstyla 3000 IU - EU/1/16/1158/007. **On medical prescription. Date of revision of the text:** 05/2019

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