1. NAME OF THE MEDICINAL PRODUCT

AFSTYLA, 500IU, lyophilized powder for injection and solvent.

AFSTYLA, 1000IU, lyophilized powder for injection and solvent.

AFSTYLA, 2000IU, lyophilized powder for injection and solvent.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

AFSTYLA 500 IU Lyophilized powder for injection and solvent: Each vial contains nominally 500 IU recombinant, single-chain coagulation factor VIII (rVIIISingleChain,INN = lonoctocog alfa). After reconstitution with 2.5 ml water for injections the solution contains 200 IU/ml of rVIII-SingleChain.

AFSTYLA 1000 IU Lyophilized powder for injection and solvent: Each vial contains nominally 1000 IU recombinant, single-chain coagulation factor VIII (rVIIISingleChain,INN = lonoctocog alfa). After reconstitution with 2.5 ml water for injections the solution contains 400 IU/ml of rVIII-SingleChain.

AFSTYLA 2000 IU Lyophilized powder for injection and solvent : Each vial contains nominally 2000 IU recombinant, single-chain coagulation factor VIII (rVIIISingleChain, INN = lonoctocog alfa). When reconstituted with 5 ml water for injections the solution contains 400 IU/ml of rVIII-SingleChain.

The potency (IU) is determined using the European Pharmacopoeia chromogenic assay. The specific activity of AFSTYLA is 7400 - 16000 IU/mg/protein.

Lonoctocog alfa is a single chain recombinant 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, the recombinant factor VIII is expressed as a single chain factor VIII molecule.

Excipient with known effect:
Sodium approximately 0.23-0.30 mmol/mL (5.4-7.0 mg/mL).

For the full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder and solvent for solution for injection.
White or slightly yellow powder or friable mass and clear, colourless solvent for solution for injection.

After reconstitution:
The solution should be almost colourless, clear or slightly opalescent.

4. CLINICAL PARTICULARS

4.1 Indications

AFSTYLA is indicated in adults and paediatrics with haemophilia A (congenital factor VIII deficiency) for:

- Control and prevention of bleeding episodes,
- Routine prophylaxis to prevent or reduce the frequency of bleeding episodes.
- Perioperative prophylaxis (surgical prophylaxis)

4.2 Posology and method of administration

Initiate treatment of AFSTYLA under the supervision of a physician experienced in the treatment of haemophilia.

The decision for an individual patient on the use of home treatment of bleeding and prophylaxis of bleeding in patients with haemophilia A should be made by the treating physician who should ensure that appropriate training is provided and the use is reviewed at intervals.

Posology
The dose and duration of the treatment depend on the severity of the factor VIII deficiency, the location and extent of the bleeding, and 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 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 an International Standard for factor VIII in plasma).

Each vial label of AFSTYLA states the factor VIII potency in International Units (IU). One IU corresponds to the activity of factor VIII contained in one millilitre 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 (see 4.4 Special Warnings and Precautions for Use).

On demand treatment
Calculation of the required dose of factor VIII is based on the empirical finding that 1 IU factor VIII per kg body weight raises the plasma factor VIII activity by 2 IU/dL. The expected *in vivo* peak increase in factor VIII level expressed as IU/dL (or % of normal) is estimated using the following formula:

Estimated Increment of factor VIII (IU/dL or % of normal) = [Total Dose (IU)/body weight (kg)] x 2 (IU/dL per IU/kg)

The dose to achieve a desired *in vivo* peak increase in factor VIII level may be calculated 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.

A guide for dosing AFSTYLA for the control and prevention of bleeding episodes is provided in the following table. Consideration should be given to maintaining a factor VIII activity at or above the target range:

Degree of haemorrhage / Type of surgical procedure	**Factor VIII level required (% or IU/dl)**	**Frequency of doses (hours) / Duration of therapy (days)**
Haemorrhage		
Early haemarthrosis, muscle bleeding or oral bleeding	20 - 40	Repeat injection every 12 - 24 hours until bleeding is resolved.
More extensive haemarthrosis, muscle bleeding or haematoma	30 - 60	Repeat injection every 12 - 24 hours until bleeding is resolved.
Life-threatening haemorrhages	60 - 100	Repeat injection every 8 - 24 hours until bleed is resolved.
Surgery		
Minor including tooth extraction	30 - 60	Repeat injection every 24 hours for at least 1 day, until healing is achieved.
Major	80 - 100 (pre- and postoperative)	Repeat injection every 8 - 24 hours until adequate wound healing, then continue therapy for at least another 7 days to maintain a factor VIII activity of 30 % - 60 % (IU/dL).

Prophylaxis

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.

Previously untreated patients (PUPs)
Overall, the safety and efficacy profile of AFSTYLA in PUPs was consistent with the benefit-risk profile reported in the previously treated patients (PTPs) except for the occurrence of neutralising antibodies, which is a recognised risk of FVIII replacement therapy in this patient population (see section 4.4).

Paediatric population
Higher and/or more frequent dosing based on body weight may be needed because clearance (based on per kg body weight) has been shown to be higher in the paediatric population (0 to 12 years of age).

Currently available data are described in section 5.2.

Geriatric population
Clinical studies of AFSTYLA did not include subjects aged over 65 years.

Monitoring for inhibitors
Patients should be monitored for the development of factor VIII inhibitors. See also section 4.4.

Method of administration
Intravenous use.

For instructions on reconstitution of the medicinal product before administration, see section 6.6. The reconstituted preparation should be injected slowly at a rate comfortable for the patient.

The patient should be observed for any immediate reaction. If any reaction takes place that might be related to the administration of AFSTYLA, the rate of injection should be decreased or the application should be stopped, as required by the clinical condition of the patient (see also section 4.4).

4.3 Contraindications

AFSTYLA is contraindicated in patients who have had life-threatening hypersensitivity reactions, including anaphylaxis to AFSTYLA or any of its components, or hamster proteins.

4.4 Warnings and precautions for use

Hypersensitivity
Allergic type hypersensitivity reactions, including anaphylaxis, are possible with AFSTYLA. Patients should be informed of the early signs of hypersensitivity reactions that may progress to anaphylaxis including hives, generalised urticaria, tightness of the chest, wheezing, hypotension and pruritus. Immediately discontinue administration and initiate appropriate treatment if hypersensitivity reactions occur.

Advise patients to discontinue use of AFSTYLA and to contact their physician.
For patients with previous hypersensitivity reactions pre-medication with antihistamines may be considered.

Neutralising antibodies
Formation of neutralising antibodies (inhibitors) to factor VIII has been reported following administration of factor VIII products, including AFSTYLA. Previously untreated patients (PUPs) are at greatest risk for inhibitor development with all Factor VIII products, including AFSTYLA.

Patients should be monitored for the development of neutralising antibodies (inhibitors) by appropriate clinical observations and laboratory tests. If expected factor VIII plasma activity level is not attained or if bleeding is not controlled after AFSTYLA administration, the presence of an inhibitor (neutralising antibody) should be suspected.
A specialised haemophilia treatment centre should be contacted if a patient develops an inhibitor.

Perform a Bethesda inhibitor assay if expected factor VIII plasma levels are not attained or if bleeding is not controlled with the expected dose of AFSTYLA. Use Bethesda Units (BU) to report inhibitor levels.

Monitoring Laboratory Tests:
Factor VIII plasma activity in patients receiving AFSTYLA can be monitored using either a chromogenic substrate assay or a one-stage clotting assay due to the consistent and predictable discrepancy in factor VIII activity measurements between the two assay formats.

Efficacy results of a large pivotal clinical study confirmed that the chromogenic substrate assay results most accurately reflect the clinical haemostatic potential. Therefore, the chromogenic substrate assay should be used to determine factor VIII activity in patient samples if available. If the one-stage method is used to determine factor VIII activity in patient samples, results should be interpreted taking into account that one-stage assay results are approximately 45% lower than those of the chromogenic substrate assay (i.e. the one-stage assay results can be aligned to chromogenic substrate acquired results by multiplying the one-stage result with 2).

It is strongly recommended that every time that AFSTYLA is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the medicinal product.

Cardiovascular events
In patients with existing cardiovascular risk factors, substitution therapy with factor VIII may increase the cardiovascular risk.

Catheter-related complications
If a central venous access device (CVAD) is required, risk of CVAD-related complications including local infections, bacteraemia and catheter site thrombosis should be considered.

Paediatric population
The listed warnings and precautions apply both to adults and children.

4.5 Interaction with other medicinal products

No interactions of AFSTYLA with other medicinal products have been reported.

4.6 Fertility, pregnancy and lactation

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

It is not known whether or not AFSTYLA is excreted into human milk. Because many drugs are excreted into human milk, caution should be exercised when AFSTYLA is administered to a nursing mother.

4.7 Effects on ability to drive and use machines

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

4.8 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) (see also 4.4). Hypersensitivity reactions were observed in clinical trials of AFSTYLA (see below ADR table), no anaphylactic reactions were reported.

Patients with haemophilia A may develop neutralising antibodies (inhibitors) to factor VIII, including AFSTYLA. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted. No such reactions have been observed in completed clinical trials in previously treated patients with AFSTYLA. Development of neutralising antibodies (inhibitors) to factor VIII was observed in the clinical trial in previously untreated patients with AFSTYLA (see below ADR table).

Tabulated list of adverse reactions
The table presented below is according to the MedDRA system organ classification (SOC and Preferred Term level).

Frequencies have been evaluated on a per patient basis based on data from completed clinical trials according to the following convention:
very common: ≥ 1/10
common: ≥ 1/100 and < 1/10
uncommon ≥ 1/1,000 and < 1/100
rare ≥ 1/10,000 and < 1/1,000
very rare < 1/10,000
not known (cannot be estimated from the available data).

MedDRA System Organ Class	**Adverse Reaction MedDRA Preferred Term**	**Frequency category acc to CIOMS**
Blood and lymphatic systems disorders	Factor VIII inhibition	uncommon (PTPs) * very common (PUPs) **
Immune system disorders	Hypersensitivity	common
Nervous system disorders	Dizziness	common
	Paraesthesia	common
Skin and subcutaneous tissue disorders	Rash	common
	Erythema	uncommon
	Pruritus	uncommon
General disorders and administration site conditions	Pyrexia	common
	Injection site pain	uncommon
	Chills	uncommon
	Feeling hot	uncommon

* PTPs - previously treated patients. Frequency of Factor VIII inhibition is based on class frequency for FVIII products.
** PUPs - previously untreated patients.
Inhibitor development has been observed in PUPs in the clinical study and in postmarketing use.In the clinical study, a majority of inhibitors resolved with continued treatment with AFSTYLA.

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:

Pusat Farmakovigilans
c.q. Direktorat Pengawasan Keamanan, Mutu, dan Ekspor Impor Obat, Narkotika,

Psikotropika, Prekursor, dan Zat Adiktif
Badan Pengawas Obat dan Makanan Republik Indonesia
Post: Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email: pv-center@pom.go.id
Tel: +62-21-4244691 Ext. 1079
Website: http://e-meso.pom.go.id/

and/or

Corporate Pharmacovigilance Dexa Group
Post: Titan Center. Jalan Boulevard Bintaro, Blok B7/B1, No.5, Bintaro Jaya, Sektor 7, Tangerang Selatan 15424, Indonesia
Email: pv@dexagroup.com
Website: www.dexagroup.com

4.9 Overdose

No symptoms of overdose with AFSTYLA have been reported. One patient was reported to have received more than double the prescribed dose. No related adverse events were reported with this overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihemorrhagics: Blood coagulation factor VIII.
ATC code: B02BD02

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

Mechanism of Action
AFSTYLA (INN: lonoctocog alfa) contains a recombinant protein that replaces the missing coagulation factor VIII needed for effective haemostasis. Lonoctocog alfa is a single chain recombinant factor VIII construct where most of the B-domain occurring in wild-type, full-length factor VIII is removed. After activation lonoctocog alfa has an amino acid sequence identical to factor VIIIa formed from endogenous, full-length factor VIII. Additionally, the single-chain design results in high binding affinity of lonoctocog alfa to von Willebrand Factor.

Pharmacodynamic effects

Haemophilia A is an x-linked hereditary disorder of blood coagulation due to decreased levels of factor VIII and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as 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.

5.2 Pharmacokinetic properties

Adult population

The pharmacokinetics (PK) of AFSTYLA were evaluated in 81 adult subjects following an intravenous injection of a single dose of 50 IU/kg.
The PK parameters were based on plasma factor VIII activity measured by the chromogenic substrate assay. The PK profile obtained 3 to 6 months after the initial PK assessment was comparable with the PK profile obtained after the first dose.

Pharmacokinetic Parameters (Arithmetic Mean, CV%) Following a Single Injection of 50 IU/kg of AFSTYLA - Chromogenic Substrate Assay:

PK Parameters	**rVIII-SingleChain 50 IU/kg (N=81)**
IR (IU/dL)/(IU/kg)	2.00 (20.8)
C_{max} (IU/dL)	106 (18.1)
AUC_{0-inf} (IU*h/dL)	1960 (33.1)
$t_{1/2}$ (h)	14.2 (26.0)
MRT (h)	20.4 (25.8)
CL (mL/h/kg)	2.90 (34.4)
V_{ss} (mL/kg)	55.2 (20.8)

IR = incremental recovery recorded at 30 minutes after injection; C_{max} = maximum concentration; AUC_{0-inf} = area under the factor VIII activity time curve extrapolated to infinity; $t_{1/2}$ = half-life; MRT = mean residence time; CL = body weight adjusted clearance; V_{ss} = body weight adjusted volume of distribution at steady-state

Paediatric population

The pharmacokinetics (PK) of AFSTYLA were evaluated in 10 adolescents (12 to <18 years of age) and 39 children (0 to <12 years of age) following an intravenous injection of a single dose of 50 IU/kg.

The PK parameters were based on plasma factor VIII activity measured by the chromogenic substrate assay.

Comparison of Pharmacokinetic Parameters by Age Category (Arithmetic Mean, CV%) Following a Single Injection of 50 IU/kg of AFSTYLA - Chromogenic Assay:

PK Parameters	**0 to <6 years (N=20)**	**6 to <12 years (N=19)**	**12 to <18 years (N=10)**
IR (IU/dL)/(IU/kg)	1.60 (21.1)	1.66 (19.7)	1.69 (24.8)

C_{max} (IU/dL)	80.2 (20.6)	83.5 (19.5)	89.7 (24.8)
AUC_{0-inf} (IU*h/dL)	1080 (31.0)	1170 (26.3)	1540 (36.5)
$t_{1/2}$ (h)	10.4 (28.7)	10.2 (19.4)	14.3 (33.3)
MRT (h)	12.4 (25.0)	12.3 (16.8)	20.0 (32.2)
CL (mL/h/kg)	5.07 (29.6)	4.63 (29.5)	3.80 (46.9)
V_{ss} (mL/kg)	71.0 (11.8)	67.1 (22.3)	68.5 (29.9)

IR = incremental recovery recorded at 30 minutes after injection for subjects 12 to < 18 years and at 60 minutes after injection for subjects 1 to < 12 years; C_{max} = maximum concentration; AUC = area under the factor VIII activity time curve extrapolated to infinity; $t_{1/2}$ = half-life; MRT = mean residence time; CL = body weight adjusted clearance; Vss = body weight adjusted volume of distribution at steady-state.

5.3 Preclinical data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single and repeated dose toxicity studies, local tolerability and thrombogenicity assessments.

5.4 Clinical studies

Safety and efficacy of AFSTYLA was evaluated in three multicentre, open-label studies in previously treated patients (PTPs): study 1001 in adolescents and adults, study 3002 in paediatric population and extension study 3001 in paediatric population, adolescents and adults. The safety and efficacy of AFSTYLA was also evaluated in previously untreated patients (PUPs) in study 3001.

Previously treated patients (PTPs)
Adult and adolescent population 12 - 65 years of age (Study 1001)
Study determined the efficacy and safety in the prevention of bleeding events in prophylaxis, haemostatic efficacy in the control of bleeding events and during perioperative management. 174 PTPs (12 to 65 years of age) with severe haemophilia A (1 subject >60 years of age) received at least one dose of AFSTYLA and accumulated a total of 14,306 EDs. No patient developed an inhibitor or experienced an anaphylactic reaction.

Prophylaxis: 146 subjects were assigned to a prophylaxis regimen (median ABR, 1.14 (interquartile range: 0.0, 4.2)), 47 (32%) were assigned to a 2-times per week regimen and 79 (54%) to a 3-times per week regimen. Patients on prophylaxis 2- and 3-times per week were assigned median doses of 35 and 30 IU/kg per injection, respectively, with a median annual consumption across all prophylaxis regimens of 4,283 IU/kg year.

Treatment of bleeding: Of the 848 bleeding events observed during Study 1001, 93.5% were controlled with 2 or fewer injections. The median dose to treat a bleeding episode was 34.7 IU/kg.

Perioperative management (surgical prophylaxis): A total of 16 major surgical procedures were performed and assessed in 13 subjects in Study 1001. Haemostatic efficacy of rVIII-SingleChain in surgical prophylaxis was rated as excellent or good in all surgeries. No paediatric subjects <18 years of age were included in the surgery population.

Paediatric population <12 years of age (Study 3002)
Study enrolled a total of 84 PTPs <12 years of age (35 subjects <6 years of age and 49 subjects 6 to <12 years of age). The study participants accumulated a total of 5,239 EDs with rVIII-SingleChain. No patient developed an inhibitor or experienced an anaphylactic reaction.

Individualised prophylaxis: Of the 80 patients on prophylaxis (median ABR 3.69 (interquartile range: 0.00, 7.20)), 43 (54%) were assigned to a 2-times weekly regimen and 24 (30%) to a 3-times per week regimen. Patients on prophylaxis 2- and 3-times per week were assigned median doses of 35 and 32 IU/kg per injection respectively with a median annual consumption across all prophylaxis regimens of 4,109 IU/kg year.

Treatment of bleeding: Of the 347 bleeding events observed during Study 3002, 95.7%were controlled with 2 or fewer injections. The median dose used to treat a bleeding event was 27.6 IU/kg.

Paediatric, adolescents and adults (Extension Study 3001)
Study 3001 enrolled 222 PTPs (67 subjects <12 years of age) including 204 PTPs from the lead-in studies 1001 and 3002. The mean (SD) number of EDs for PTPs in this study was 341.9 (135.48). A total 212 subjects (95.5%) attained > 100 EDs. No patient developed an inhibitor or experienced an anaphylactic reaction. No new safety concerns were identified from this extension study. Results on individualised prophylaxis and treatment of bleeding were comparable to what was reported in earlier studies.

Individualised prophylaxis: Of the 211 patients on prophylaxis (median ABR (1.21 (interquartile range: 0.33, 3.03)), 85 (40%) were assigned to a 2-times weekly regimen and 97 (46%) to a 3-times per week regimen. Patients on prophylaxis 2- and 3-times per week were assigned median doses of 35 and 32 IU/kg per injection respectively with a median annual consumption across all prophylaxis regimens of 4,603 IU/kg year.

Treatment of bleeding: Of the 2413 treated bleeding events observed during Study 3001, 86.3% were controlled with 2 or fewer injections.

Previously untreated patients (PUPs)
Paediatric population <12 years of age (Study 3001)
Study enrolled a total of 24 PUPs with a median age of 1.0 years (range:0 to 5 years). The study participants accumulated a total of 5909 EDs with rVIII-SingleChain.

Individualised prophylaxis: A total of 23 PUPs received the prophylactic regimen during the study (11 switched from on-demand). Median ABR was 1.84 (range: 0.0 to 23.6), median AsBR was 0.88 (range: 0.0 to 19.7).

Treatment of bleeding: Of the 315 treated bleeding events, 88.9% were controlled with 2 or fewer injections. The median dose used to treat a bleeding event was 66.2 IU/kg.

Overall, the benefit-risk profile of AFSTYLA in PUPs was consistent with the benefit-risk profile reported in PTPs except for the occurrence of neutralising antibodies, which is a

recognised risk of FVIII replacement therapy in PUPs.

Data on Immune Tolerance Induction (ITI) have been collected in patients with haemophilia A who had developed inhibitors to factor VIII. During clinical trial in PUPs, 11 patients were treated with ITI with AFSTYLA and 9 patients achieved immune tolerance shown by a negative inhibitor test result at completion of the study.

Of note, annualised bleeding rate (ABR) is not comparable between different factor concentrates and between different clinical studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

L-Histidine
Polysorbate 80
Calcium chloride di-hydrate
Sodium chloride
Sucrose
Hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products, diluents or solvents except those mentioned in section 2. and 6.5.

6.3 Shelf life

36 months.

After reconstitution the chemical and physical in-use stability has been demonstrated for 48 hours at room temperature (below 25 °C). From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use should not be longer than 4 hours up to 25 °C.

6.4 Precautions for storage

Store in a refrigerator at 2°C to 8°C.
Do not freeze. Keep vials in the outer carton in order to protect from light.

AFSTYLA may be stored at room temperature, not to exceed 25°C (77°F), for a single period of up to 3 months, within the expiration date printed on the carton and vial labels.

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

6.5 Nature and contents of container

Immediate containers
Powder (500/1000/2000 IU) in a vial (type I glass), with a stopper (rubber) a disc (plastic) and a cap (aluminium).
2.5/5 mL of solvent in a vial (type I glass), with a stopper (rubber) a disc (plastic) and a cap (aluminium).

Presentation
Box containing:
Powder vial
Solvent vial
Filter transfer device 20/20 (Mix2Vial)
Administration set (inner box):
- venipuncture set
- alcohol swab
- disposable syringe

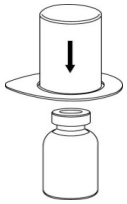
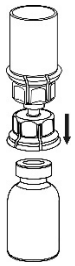
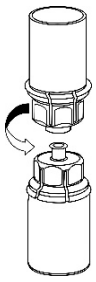
Not all pack sizes may be marketed.

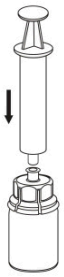
6.6 Instruction for use and other handling

General instructions
- The solution should be almost colourless, clear or slightly opalescent. After filtering/withdrawal (see below) the reconstituted product should be inspected visually for particulate matter and discoloration prior to administration.
- Do not use visibly cloudy solutions or solutions still containing flakes or particles.
- Reconstitution and withdrawal must be carried out under aseptic conditions.

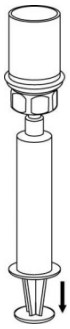
Reconstitution
Bring the solvent to room temperature. Ensure AFSTYLA and solvent vial flip caps are removed and the stoppers are treated with an antiseptic solution and allowed to dry prior to opening the Mix2Vial package.

 1	1. Open the Mix2Vial package by peeling off the lid. Do **not** remove the Mix2Vial from the blister package!

 2	2. Place the **solvent vial** on an even, clean surface and hold the vial tight. Take the Mix2Vial together with the blister package and push the spike of the **blue** adapter end **straight down** through the solvent vial stopper.
 3	3. Carefully remove the blister package from the Mix2Vial set by holding at the rim, and pulling **vertically** upwards. Make sure that you only pull away the blister package and not the Mix2Vial set.
 4	4. Place the **AFSTYLA vial** on an even and firm surface. Invert the solvent vial with the Mix2Vial set attached and push the spike of the **transparent** adapter end **straight down** through the AFSTYLA vial stopper. The solvent will automatically flow into the AFSTYLA vial.
 5	5. With one hand grasp the AFSTYLA side of the Mix2Vial set and with the other hand grasp the solvent-side and unscrew the set carefully counterclockwise into two pieces. Discard the solvent vial with the blue Mix2Vial adapter attached.
 6	6. Gently swirl the AFSTYLA vial with the transparent adapter attached until the substance is fully dissolved. Do not shake.

 7	7. Draw air into an empty, sterile syringe. While the AFSTYLA vial is upright, connect the syringe to the Mix2Vial's Luer Lock fitting by screwing clockwise. Inject air into the AFSTYLA vial.

Withdrawal and application

 8	8. While keeping the syringe plunger pressed, turn the system upside down and draw the solution into the syringe by pulling the plunger back slowly.
 9	9. Now that the solution has been transferred into the syringe, firmly hold on to the barrel of the syringe (keeping the syringe plunger facing down) and disconnect the transparent Mix2Vial adapter from the syringe by unscrewing counterclockwise.

For injection of AFSTYLA the provided administration sets are recommended to be used because treatment failure can occur as a consequence of factor VIII adsorption to the internal surface of some injection equipment.

Care should be taken that no blood enters the syringe filled with product, as there is a risk that the blood could coagulate in the syringe and fibrin clots could therefore be administered to the patient.

The AFSTYLA solution must not be diluted.

The reconstituted solution should be administered by a separate injection/infusion line by slow intravenous injection, at a rate comfortable to the patient.

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

7. Manufacturer

CSL Behring GmbH
Emil-von-Behring-Str. 76
35041 Marburg
Germany

Imported and Marketed by:
PT Dexa Medica
Palembang – Indonesia

8. MARKETING AUTHORISATION NUMBER(S)

DKIXXXXXXXXXXXX

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

DD Month YYYY

10. DATE OF REVISION OF THE TEXT

Date of last revision: May 2026

HARUS DENGAN RESEP DOKTER
ON MEDICAL PRESCRIPTION ONLY

AFSTYLA

Lonoctocog alfa

Serbuk liofilisasi untuk injeksi dan pelarut 500 IU, 1.000 IU & 2.000 IU

Baca seluruh isi *leaflet* dengan cermat sebelum Anda menggunakan obat ini karena di dalam *leaflet* ini terdapat informasi penting untuk Anda.

- Simpan *leaflet* ini, mungkin suatu saat Anda perlu membacanya kembali.
- Apabila Anda memiliki pertanyaan lebih lanjut, tanyakan pada dokter atau apoteker.
- Obat ini hanya diresepkan untuk Anda. Tidak boleh memberikan obat ini pada orang lain karena akan membahayakan, meskipun orang tersebut memiliki gejala yang sama seperti Anda.
- Apabila muncul efek samping, segera hubungi dokter atau apoteker. Termasuk efek samping yang tidak tercantum di dalam *leaflet* ini.

Apa saja yang terdapat pada *leaflet* ini:

1. Apa itu AFSTYLA dan apa kegunaannya

Apa itu AFSTYLA

AFSTYLA adalah produk faktor pembekuan (koagulasi) VIII yang diberikan melalui injeksi dan diproduksi dengan teknologi DNA rekombinan. Zat aktif dalam AFSTYLA adalah *lonoctocog alfa*.

Bagaimana AFSTYLA bekerja

Faktor VIII berperan dalam proses pembekuan darah. Kekurangan faktor ini menyebabkan darah tidak dapat membeku secepat yang seharusnya, sehingga meningkatkan kecenderungan terjadinya perdarahan. AFSTYLA bekerja dengan menggantikan faktor VIII pada pasien hemofilia A sehingga memungkinkan darah membeku dengan normal.

Apa kegunaan AFSTYLA

AFSTYLA digunakan untuk mengobati dan mencegah episode perdarahan pada pasien dengan hemofilia A (defisiensi faktor VIII bawaan) dan dapat digunakan untuk semua usia.

2. Apa yang perlu Anda ketahui sebelum menggunakan AFSTYLA

Bacalah bagian berikut dengan saksama. Informasi yang diberikan harus dipertimbangkan oleh Anda dan dokter sebelum Anda menggunakan AFSTYLA.

AFSTYLA tidak boleh digunakan:

Jika Anda pernah mengalami reaksi alergi yang mengancam jiwa terhadap AFSTYLA, salah satu komponen atau bahan lainnya (lihat **Isi kemasan dan informasi lainnya**), atau protein hamster.

Peringatan dan perhatian

Beritahukan kepada dokter Anda atau tenaga kesehatan profesional sebelum menggunakan AFSTYLA.

- Reaksi alergi (hipersensitivitas) dapat terjadi. Produk ini mengandung protein hamster (lihat **AFSTYLA tidak boleh digunakan**). Jika gejala hipersensitivitas muncul, segera hentikan penggunaan obat dan hubungi dokter. Dokter akan memberi tahu Anda tanda-tanda awal reaksi hipersensitivitas, termasuk urtikaria (biduran), ruam kulit menyeluruh, rasa sesak di dada, mengi, penurunan tekanan darah, dan anafilaksis (reaksi alergi berat yang menyebabkan kesulitan bernapas atau pusing berat)
- Karena adanya risiko reaksi alergi terhadap faktor VIII, pemberian awal AFSTYLA harus dilakukan di bawah pengawasan tenaga kesehatan sehingga penanganan yang tepat dapat segera diberikan jika terjadi reaksi alergi.
- Pembentukan inhibitor (antibodi penetral) merupakan komplikasi yang diketahui dapat terjadi selama pengobatan, yang dapat menyebabkan terapi menjadi tidak efektif. Jika perdarahan Anda

tidak terkontrol setelah penggunaan AFSTYLA, segera beritahu dokter. Anda harus dipantau secara ketat terhadap kemungkinan perkembangan inhibitor.
- Jika Anda atau anak Anda memiliki penyakit jantung atau berisiko mengalami penyakit jantung, beri tahu dokter atau apoteker.
- Jika digunakan alat akses vena sentral (*central venous access device*/CVAD) untuk injeksi AFSTYLA, terdapat risiko komplikasi termasuk infeksi lokal, bakteri dalam darah (bakteremia), serta pembentukan bekuan darah (trombosis) pada pembuluh darah.

Catatan penggunaan
Sangat dianjurkan untuk mencatat di dalam buku catatan terapi Anda terkait tanggal pemberian, nomor bets, dan volume yang disuntikkan setiap kali AFSTYLA diberikan.

Obat lain dan AFSTYLA
Beritahu dokter atau apoteker jika Anda sedang menggunakan, baru saja menggunakan, atau mungkin akan menggunakan obat lain.

Kehamilan dan menyusui
- Jika Anda sedang hamil atau menyusui, menduga bahwa mungkin sedang hamil, atau merencanakan kehamilan, mintalah saran dokter atau apoteker sebelum menggunakan obat ini
- Selama kehamilan dan menyusui, AFSTYLA hanya boleh diberikan jika benar-benar diperlukan.

Kemampuan mengemudi dan mengoperasikan mesin
AFSTYLA tidak memengaruhi kemampuan Anda untuk mengemudi dan menggunakan mesin.

AFSTYLA mengandung natrium
AFSTYLA mengandung natrium hingga 7,0 mg (0,30 mmol) per ml setelah rekonstitusi.

3. Bagaimana cara penggunaan AFSTYLA

Pengobatan Anda harus dimulai dan dipantau oleh dokter yang berpengalaman dalam penanganan gangguan pembekuan darah.

Apabila dokter menilai bahwa Anda dapat menggunakan AFSTYLA secara mandiri, Anda akan diberikan petunjuk yang sesuai. Gunakan AFSTYLA persis seperti instruksi yang diberikan oleh dokter Anda. Konsultasikan dengan dokter jika Anda tidak yakin.

Dosis
Dokter akan menghitung dosis AFSTYLA yang Anda butuhkan. Jumlah dosis dan lama pengobatan bergantung pada:
- tingkat keparahan penyakit Anda
- lokasi dan tingkat keparahan perdarahan
- kondisi klinis dan respons Anda terhadap terapi
- berat badan Anda

Ikuti petunjuk yang diberikan oleh dokter Anda.

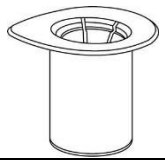
Rekonstitusi dan cara pemberian
Petunjuk umum
- Serbuk harus dicampur dengan pelarut (cairan) dan diambil dari vial dalam kondisi aseptik.
- AFSTYLA tidak boleh dicampur dengan obat lain, pengencer, atau pelarut selain yang disebutkan pada **Isi kemasan dan informasi lainnya**.
- Larutan harus jernih atau sedikit opalesen, berwarna kuning hingga tidak berwarna, dan dapat tampak berkilau saat terkena cahaya, namun tidak boleh mengandung partikel yang terlihat. Setelah penyaringan atau pengambilan (lihat di bawah), larutan harus diperiksa secara visual sebelum digunakan. Jangan gunakan larutan jika tampak keruh atau mengandung serpihan atau partikel.
- Sisa produk yang tidak terpakai atau limbah harus dibuang sesuai dengan ketentuan setempat dan petunjuk dokter.

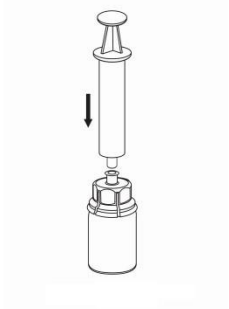
Rekonstitusi

Tanpa membuka vial, hangatkan serbuk AFSTYLA dan cairan pelarut hingga suhu ruang atau suhu tubuh. Hal ini dapat dilakukan dengan membiarkan vial pada suhu ruang selama sekitar satu jam, atau dengan memegangnya di tangan selama beberapa menit.

JANGAN memaparkan vial pada panas langsung. Vial tidak boleh dipanaskan melebihi suhu tubuh (37°C).

Lepaskan penutup pelindung dari vial dengan hati-hati, kemudian bersihkan penutup karet yang terbuka menggunakan*alcohol swab*. Biarkan vial mengering sebelum membuka kemasan *Mix2Vial* (yang berisi alat transfer dengan filter), kemudian ikuti petunjuk penggunaan berikutnya.

1 	Buka kemasan *Mix2Vial* dengan mengelupas penutupnya. Jangan keluarkan *Mix2Vial* dari kemasan *blister!*
2 	Letakkan **vial pelarut** pada permukaan yang rata dan bersih, lalu pegang vial dengan kuat. Ambil *Mix2Vial* beserta kemasan *blister* dan tekan ujung adaptor berwarna **biru** secara **tegak lurus** menembus penutup vial pelarut.
3 	Perlahan lepaskan kemasan *blister* dari set *Mix2Vial* dengan memegang bagian tepinya, lalu tarik ke atas **secara vertikal**. Pastikan yang dilepas hanya kemasan *blister*, bukan set *Mix2Vial*.
4 	Letakkan **vial AFSTYLA** pada permukaan yang rata dan stabil. Balikkan vial pelarut dengan set *Mix2Vial* yang terpasang, lalu tekan ujung (*spike*) adaptor **transparan** secara **tegak lurus** menembus penutup vial AFSTYLA. Pelarut akan secara otomatis mengalir ke dalam vial AFSTYLA.
5 	Dengan satu tangan, pegang bagian vial AFSTYLA dari set *Mix2Vial* dan dengan tangan lainnya pegang bagian vial pelarut, kemudian putar berlawanan arah jarum jam secara perlahan untuk memisahkan vial menjadi dua bagian. Buang vial pelarut beserta adaptor *Mix2Vial* berwarna biru yang terpasang.
6 	Putar perlahan vial AFSTYLA dengan adaptor transparan yang terpasang hingga seluruh serbuk larut sempurna. Jangan dikocok.

7 	Tarik udara ke dalam spuit steril yang kosong. Dengan vial AFSTYLA dalam posisi tegak, hubungkan spuit ke konektor *Luer Lock* pada *Mix2Vial* dengan memutar searah jarum jam. Suntikkan udara ke dalam vial AFSTYLA.

Pengambilan dan pemberian larutan

8 	Dengan tetap menekan *plunger* spuit, balikkan sistem, kemudian ambil larutan ke dalam spuit dengan menarik *plunger* secara perlahan.
9 	Setelah larutan seluruhnya berpindah ke dalam spuit, pegang badan spuit dengan kuat (dengan posisi *plunger* menghadap ke bawah), lalu lepaskan adaptor transparan *Mix2Vial* dari spuit dengan memutar berlawanan arah jarum jam.

Gunakan set venipunktur yang disediakan bersama produk, kemudian masukkan jarum ke dalam vena. Biarkan darah mengalir kembali hingga mencapai ujung selang. Pasang spuit pada ujung berulir yang dapat dikunci pada set venipunktur. **Suntikkan larutan yang telah direkonstitusi secara perlahan (sesuai kenyamanan Anda) ke dalam vena** mengikuti petunjuk yang diberikan oleh dokter. Pastikan tidak ada darah yang masuk ke dalam spuit yang berisi produk.

Amati adanya efek samping yang mungkin muncul segera setelah pemberian. Jika Anda mengalami efek samping yang diduga berkaitan dengan pemberian AFSTYLA, injeksi harus segera dihentikan (lihat juga **Apa yang perlu Anda ketahui sebelum menggunakan AFSTYLA**).

Penggunaan pada anak dan remaja
AFSTYLA dapat digunakan pada anak-anak dari semua kelompok usia. Pada anak-anak (di bawah usia 12 tahun), mungkin diperlukan dosis yang lebih tinggi atau frekuensi injeksi yang lebih sering.

Apa tanda dan gejala kelebihan dosis?
Jika Anda telah menyuntikkan AFSTYLA lebih banyak dari yang seharusnya, segera beritahu dokter Anda. **(III)**

Jika Anda memiliki pertanyaan lebih lanjut mengenai penggunaan obat ini, tanyakan kepada dokter, apoteker, atau perawat.

4. Efek samping yang mungkin terjadi

Seperti obat-obat lainnya, AFSTYLA dapat menyebabkan efek samping, meskipun tidak semua orang

mengalaminya.

Segera hubungi dokter dalam keadaan darurat apabila:
- **Anda mengalami gejala reaksi alergi (lihat di bawah)**
- **Anda merasa obat tidak bekerja dengan baik**

Efek samping umum (dapat terjadi pada hingga 1 dari 10 pasien)
- reaksi alergi
- pusing
- kesemutan atau baal (parestesia)
- ruam
- demam

Efek samping tidak umum (dapat terjadi pada hingga 1 dari 100 pasien)
- gatal
- kemerahan pada kulit
- nyeri di tempat suntikan
- menggigil
- rasa panas

Efek samping berikut umumnya telah diamati pada produk faktor VIII, termasuk AFSTYLA:
- Reaksi hipersensitivitas tipe alergi dapat terjadi, dengan gejala seperti: biduran, urtikaria menyeluruh, rasa sesak di dada, mengi, hipotensi, dan anafilaksis. Jika hal ini terjadi, segera hentikan penggunaan obat dan hubungi dokter. Reaksi alergi telah diamati dalam uji klinik dengan AFSTYLA.
- Inhibitor: obat menjadi tidak bekerja dengan baik (perdarahan berlanjut). Anda dapat membentuk inhibitor (antibodi penetral) terhadap faktor VIII, termasuk AFSTYLA, sehingga faktor VIII tidak lagi bekerja dengan efektif. Jika hal ini terjadi, segera hentikan penggunaan obat dan hubungi dokter. Tidak ada reaksi seperti yang disebutkan yang diamati dalam uji klinik yang telah selesai pada pasien yang sebelumnya telah mendapat terapi dengan AFSTYLA. Perkembangan inhibitor telah diamati pada pasien yang sebelumnya belum pernah mendapatkan terapi, dan pasien ini memiliki risiko terbesar untuk mengalami pembentukan inhibitor.

Efek samping pada anak-anak dan remaja
Efek samping pada anak-anak diperkirakan sama seperti pada orang dewasa.

Melaporkan efek samping
Apabila Anda mengalami salah satu efek samping tersebut, sampaikan pada dokter Anda atau tenaga kesehatan profesional. Termasuk kemungkinan efek samping yang tidak tercantum dalam *leaflet*. Dengan melaporkan efek samping, Anda dapat membantu memberikan informasi lebih lanjut terkait keamanan obat ini.

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5. Bagaimana cara penyimpanan AFSTYLA

- Jangan gunakan AFSTYLA setelah tanggal kedaluwarsa yang tertera pada label dan kemasan.
- Simpan di dalam refrigerator pada suhu 2°C hingga 8°C.
- Sebelum direkonstitusi, serbuk AFSTYLA dapat disimpan pada suhu ruang (di bawah 25°C) untuk satu periode tidak lebih dari 3 bulan, selama masih dalam batas tanggal kedaluwarsa yang tercantum pada kemasan dan vial. Catat tanggal saat Anda mulai menyimpan pada suhu ruang di kemasan produk. Jangan dibekukan.
- Simpan vial di dalam kemasan luar untuk melindungi dari cahaya.
- Produk yang telah direkonstitusi sebaiknya digunakan segera.
- Jika produk yang telah direkonstitusi tidak segera digunakan, waktu dan kondisi penyimpanan sebelum penggunaan tidak boleh melebihi 4 jam pada suhu ruang (di bawah 25°C).

6. Isi kemasan dan informasi lainnya

Apa isi kandungan AFSTYLA

AFSTYLA 500 IU

Tiap vial AFSTYLA 500 IU mengandung *lonoctocog alfa* 500 IU. Setelah direkonstitusi dengan 2,5 ml *water for injection*, larutan mengandung *lonoctocog alfa* 200 IU/ml.

AFSTYLA 1.000 IU

Tiap vial AFSTYLA 1.000 IU mengandung *lonoctocog alfa* 1.000 IU. Setelah direkonstitusi dengan 2,5 ml *water for injection*, larutan mengandung *lonoctocog alfa* 400 IU/ml.

AFSTYLA 2.000 IU

Tiap vial AFSTYLA 2.000 IU mengandung *lonoctocog alfa* 2.000 IU. Setelah direkonstitusi dengan 5 ml *water for injection*, larutan mengandung *lonoctocog alfa* 400 IU/ml.

Bahan lainnya:

Serbuk: *L-histidine*, *polysorbate* 80, *calcium chloride dihydrate*, *sodium chloride*, *sucrose*, *hydrochloric acid* (sebagai pengatur pH).
Pelarut: *water for injection*

Seperti apa AFSTYLA dan isi kemasannya

AFSTYLA berupa serbuk berwarna putih atau sedikit kekuningan atau massa rapuh, serta pelarut jernih, tidak berwarna untuk larutan untuk injeksi.

Larutan yang telah direkonstitusi harus jernih hingga sedikit opalesen, berwarna kuning hingga tidak berwarna, dan dapat tampak berkilau saat terkena cahaya, namun tidak boleh mengandung partikel yang terlihat.

Satu set kemasan berisi:

- Vial serbuk
- Vial pelarut
- Alat transfer dengan filter 20/20 (*Mix2Vial*)
- Set untuk pemberian (kotak dalam) berisi set venipunktur, *alcohol swab*, dan spuit sekali pakai.

Kemasan dan Nomor Izin Edar:
AFSTYLA 500 IU: Kotak, 1 vial serbuk liofilisasi + 1 vial pelarut; DKIXXXXXXXXXXXX
AFSTYLA 1.000 IU: Kotak, 1 vial serbuk liofilisasi + 1 vial pelarut; DKIXXXXXXXXXXXX
AFSTYLA 2.000 IU: Kotak, 1 vial serbuk liofilisasi + 1 vial pelarut; DKIXXXXXXXXXXXX

HARUS DENGAN RESEP DOKTER.

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***Date of review*:** (13 Mei 2026)

Literatur:

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