1. NAME OF THE MEDICINAL PRODUCT

AFSTYLA 250 IU powder and solvent for solution for injection

AFSTYLA 500 IU powder and solvent for solution for injection

AFSTYLA 1000 IU powder and solvent for solution for injection

AFSTYLA 2000 IU powder and solvent for solution for injection

AFSTYLA 3000 IU powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

AFSTYLA 250 IU powder and solvent for solution for injection
Each vial contains nominally 250 IU recombinant, single-chain coagulation factor VIII (rVIII-SingleChain, INN = lonoctocog alfa). After reconstitution with 2.5 ml water for injections the solution contains 100 IU/ml of rVIII-SingleChain.

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

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

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

AFSTYLA 3000 IU powder and solvent for solution for injection
Each vial contains nominally 3000 IU recombinant, single-chain coagulation factor VIII (rVIII-SingleChain, INN = lonoctocog alfa). When reconstituted with 5 ml water for injections the solution contains 600 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.

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.

Excipient with known effect:

AFSTYLA 250, 500 and 1000 IU (2.5 ml solvent)

Each vial contains 17.5 mg (0.76 mmol) of sodium.

AFSTYLA 2000 and 3000 IU (5 ml solvent)
Each vial contains 35 mg (1.52 mmol) of sodium.

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.

pH: 6.6 - 7.3

Osmolality: 500 - 600 mOsm/kg

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency).

AFSTYLA can be used for all age groups.

4.2 Posology and method of administration

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).

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.

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 section 5.2).

Elderly
Clinical studies of AFSTYLA did not include subjects over 65 years of age.

Method of administration
Intravenous use.

The reconstituted preparation should be injected slowly at a rate comfortable for the patient at a maximum injection rate of 10 ml/min.
For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Known allergic reaction to hamster proteins.

4.4 Special warnings and precautions for use

Traceability
In order to improve traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Hypersensitivity
Allergic type hypersensitivity reactions are possible with AFSTYLA. The product contains traces of hamster proteins. If symptoms of hypersensitivity occur, patients should be advised to discontinue use of the medicinal product immediately and contact their physician. Patients should be informed of the early signs of hypersensitivity reactions including hives, generalised urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis.

For patients with previous hypersensitivity reactions appropriate pre-medication may be considered.

In case of shock, standard medical treatment for shock should be implemented.

Inhibitors
The formation of neutralising antibodies (inhibitors) to factor VIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against the factor VIII procoagulant activity, which are quantified in Bethesda Units (BU) per ml of plasma using the modified assay. The risk of developing inhibitors is correlated to the severity of the disease as well as the exposure to factor VIII, this risk being highest within the first 50 exposure days but continues throughout life although the risk is uncommon.

The clinical relevance of inhibitor development will depend on the titre of the inhibitor, with low titre posing less of a risk of insufficient clinical response than high titre inhibitors.

In general, all patients treated with coagulation factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII inhibitor presence 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.

Monitoring laboratory tests
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 (see section 4.2).

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.

Sodium content
This medicine contains up to 7 mg (0.3 mmol) sodium per ml after reconstitution. To be taken into consideration by patients on a controlled sodium diet.

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

4.5 Interaction with other medicinal products and other forms of interaction

No interactions of human coagulation factor VIII products with other medicinal products have been reported.

4.6 Fertility, pregnancy and lactation

Animal reproduction studies have not been conducted with factor VIII. Based on the rare occurrence of haemophilia A in women, experience regarding the use of factor VIII during pregnancy and breast-feeding is not available. Therefore, factor VIII should be used during pregnancy and lactation only if clearly indicated.

4.7 Effects on ability to drive and use machines

AFSTYLA has no influence on the ability to drive and use machines.

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).

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.

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

MedDRA System Organ Class	**Adverse reaction**	**Frequency**
Blood and lymphatic system disorders	FVIII 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

*Frequency is based on studies with all FVIII products which included patients with severe haemophilia A. PTPs = previously-treated patients, PUPs = previously-untreated patients.

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.

4.9 Overdose

In a completed clinical trial a patient who received more than double the prescribed dose of AFSTYLA experienced dizziness, feeling hot, and itching not considered related to AFSTYLA but more plausibly attributed to co-administration of an analgesic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Mechanism of Action

AFSTYLA (INN: lonoctocog alfa) is a recombinant human protein that replaces the missing coagulation factor VIII needed for effective hemostasis. AFSTYLA is a single polypeptide chain with a truncated B-domain that allows for a covalent bridge to link the factor VIII heavy and light chains. AFSTYLA has demonstrated a higher VWF affinity relative to full-length rFVIII. VWF stabilizes factor VIII and protects it from degradation. Activated AFSTYLA has an amino acid sequence identical to endogenous FVIIIa.

Pharmacodynamic effects

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.
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.

Clinical efficacy and safety

Adult and adolescent population 12 - 65 years of age
Study 1001 determined the efficacy and safety in the prevention of bleeding events in prophylaxis, hemostatic efficacy in the control of bleeding events and during perioperative management. The study enrolled 175 previously treated patients (12 to 65 years of age) with severe haemophilia A (1 subject >60 years of age was enrolled) who accumulated a total of 14,306 EDs with rVIII-SingleChain. 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)), 79 (54%) were assigned a 3-times per week regimen and 47 (32%) a 2-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. Hemostatic 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 enrolled a total of 84 previously treated patients <12 years of age (35 <6 years of age and 49 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 81 patients on prophylaxis (median ABR 3.69 (interquartile range: 0.00, 7.20)), 43 (53%) were assigned to a 2-times weekly regimen and 25 (31%) 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

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

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with AFSTYLA in the treatment of hereditary factor VIII deficiency in previously untreated paediatric patients (PUPs) (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Adult population

The pharmacokinetics (PK) of AFSTYLA was evaluated in 81 previously treated adult subjects who had been diagnosed with severe haemophilia A with <1% factor VIII and with age from 18-60 years old, following an intravenous injection of 50 IU/kg.

The PK parameters were based on plasma factor VIII activity measured by the chromogenic substrate assay (for discrepancy in the factor VIII activity determined with one-stage clotting assay, please see section 4.2).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 following a Single Injection of 50 IU/kg of AFSTYLA - Chromogenic Substrate Assay:

PK Parameters	**rVIII-SingleChain 50 IU/kg (N=81) Mean (CV%) Median (Min,Max)**
IR (IU/dl)/(IU/kg)	2.00 (20.8) 1.99 (0.868, 2.90)
C_{max} (IU/dl)	106 (18.1) 106 (62.4, 151)
$AUC_{0\text{-}inf}$ (IU*h/dl)	1960 (33.1) 1910 (932, 4090)
$t_{1/2}$ (h)	14.2 (26.0) 13.7 (7.54, 23.9)
MRT (h)	20.4 (25.8) 20.2 (10.8, 35.1)
CL (ml/h/kg)	2.90 (34.4) 2.67 (1.26, 5.79)
V_{ss} (ml/kg)	55.2 (20.8) 53.2 (32.4, 99.6)

IR = incremental recovery recorded at 30 minutes after injection; C_{max} = maximum concentration, $AUC_{0\text{-}inf}$ = 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 with N = 80; V_{ss} = body weight adjusted volume of distribution at steady-state. IR and C_{max} were baseline corrected while the remaining parameters were not baseline corrected with N = 81.

Paediatric population

The pharmacokinetics (PK) of AFSTYLA were evaluated in 10 previously treated adolescents (12 to <18 years of age) and 39 previously treated children (0 to <12 years of age) following an intravenous injection of a single dose of 50 IU/kg. All patients had been diagnosed with severe haemophilia A with <1% factor VIII.

The PK parameters were based on plasma factor VIII activity measured by the chromogenic substrate assay (for discrepancy in the factor VIII activity determined with one-stage clotting assay, please see Section 4.2).

Comparison of Pharmacokinetic Parameters by Age Category following a Single Injection of 50 IU/kg of AFSTYLA - Chromogenic Assay:

PK Parameters	**0 to <6 years (N=20) Mean (CV%) Median (Min,Max)**	**6 to <12 years (N=19) Mean (CV%) Median (Min,Max)**	**12 to <18 years (N=10) Mean (CV%) Median (Min,Max)**
IR (IU/dl)/(IU/kg)	1.60 (21.1) 1.55 (1.18, 2.76)	1.66 (19.7) 1.69 (0.92, 2.35)	1.69 (24.8) 1.76 (0.88, 2.44)
C_{max} (IU/dl)	80.2 (20.6) 78.6 (59.3, 138)	83.5 (19.5) 84.5 (46.4, 117)	89.7 (24.8) 92.4 (45.5, 131)
$AUC_{0\text{-}inf}$ (IU*h/dl)	1080 (31.0) 985 (561, 2010)	1170 (26.3) 1120 (641, 1810)	1540 (36.5) 1520 (683, 2380)
$t_{1/2}$ (h)	10.4 (28.7) 10.1 (5.19, 17.8)	10.2 (19.4) 10.0 (6.92, 14.8)	14.3 (33.3) 13.5 (6.32, 23.8)
MRT (h)	12.4 (25.0) 13.0 (6.05, 17.9)	12.3 (16.8) 12.8 (8.22, 16.0)	20.0 (32.2) 18.6 (9.17, 31.7)
CL (ml/h/kg)	5.07 (29.6) 5.08 (2.52, 8.92)	4.63 (29.5) 4.48 (2.79, 7.71)	3.80 (46.9) 3.31 (2.10, 7.32)
V_{ss} (ml/kg)	71.0 (11.8) 70.7 (57.3, 88.3)	67.1 (22.3) 64.9 (44.3, 111)	68.5 (29.9) 62.0 (45.9, 121)

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; V_{ss} = body weight adjusted volume of distribution at steady-state. IR and C_{max} were baseline corrected while the remaining parameters were not baseline corrected.

5.3 Preclinical safety 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
L-Histidine, Polysorbate 80, Calcium chloride dihydrate, Sodium chloride, Sucrose

Solvent:
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

3 years.

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 are in the responsibility of the user.

6.4 Special precautions for storage

Store in a refrigerator (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, for a single period of up to 3 months, within the expiration date printed on the carton and vial labels. Once the product has been taken out of the refrigerator, the product must not be returned to the refrigerator. Please record the beginning of storage at room temperature on the product carton.

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

6.5 Nature and contents of container

AFSTYLA 250 IU powder and solvent for solution for injection
Powder (250 IU) in a 6 ml vial (type I glass) with a stopper (rubber), an orange disc (plastic), and a green striped cap (aluminium).
2.5 ml of solvent in a vial (type I glass) with a stopper (rubber), a disc (plastic), and a cap (aluminium).

AFSTYLA 500 IU powder and solvent for solution for injection
Powder (500 IU) in a 6 ml vial (type I glass) with a stopper (rubber), a blue disc (plastic), and a green striped cap (aluminium).
2.5 ml of solvent in a vial (type I glass) with a stopper (rubber), a disc (plastic), and a cap (aluminium).

AFSTYLA 1000 IU powder and solvent for solution for injection
Powder (1000 IU) in a 6 ml vial (type I glass) with a stopper (rubber), a green disc (plastic), and a green striped cap (aluminium).
2.5 ml of solvent in a vial (type I glass) with a stopper (rubber), a disc (plastic), and a cap (aluminium).

AFSTYLA 2000 IU powder and solvent for solution for injection
Powder (2000 IU) in a 10 ml vial (type I glass) with a stopper (rubber), a purple disc (plastic), and a green striped cap (aluminium).
5 ml of solvent in a vial (type I glass) with a stopper (rubber), a disc (plastic), and a cap (aluminium).

AFSTYLA 3000 IU powder and solvent for solution for injection
Powder (3000 IU) in a 10 ml vial (type I glass) with a stopper (rubber), a yellow disc (plastic), and a green striped cap (aluminium).
5 ml of solvent in a vial (type I glass) with a stopper (rubber), a disc (plastic), and a cap (aluminium).

Presentations
One pack with 250, 500 or 1000 IU containing:
1 vial with powder
1 vial with 2.5 ml water for injections
1 filter transfer device 20/20
One inner box containing:
1 disposable 5 ml syringe
1 venipuncture set
2 alcohol swabs
1 non- sterile plaster

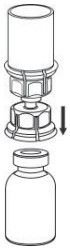
One pack with 2000 or 3000 IU containing:
1 vial with powder
1 vial with 5 ml water for injections
1 filter transfer device 20/20
One inner box containing:
1 disposable 10 ml syringe
1 venipuncture set
2 alcohol swabs
1 non- sterile plaster

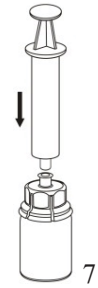
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

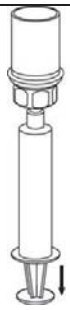
General instructions
- The solution should be almost colourless, clear or slightly opalescent. After filtering/withdrawal (see below) the reconstituted product should be inspected visually for particulate matter and discoloration prior to administration.
- Do not use visibly cloudy solutions or solutions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

Reconstitution and administration
Bring the solvent to room temperature. Ensure powder 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 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 **powder 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 powder vial stopper. The solvent will automatically flow into the powder vial.

 5	5. With one hand grasp the product-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 product 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 product vial is upright, connect the syringe to the Mix2Vial's Luer Lock fitting by screwing clockwise. Inject air into the product vial.

Withdrawal and administration

 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, up to a maximum of 10 ml/min.

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

7. Manufactured by

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

Imported by
ZUELLIG PHARMA LTD.
Bangkok, Thailand

8. MARKETING AUTHORIZATION NUMBER(S)

AFSTYLA (250 IU, 500 IU, 1000 IU, 2000 IU, 3000 IU) REG XXXXX

9. DATE OF REVISION OF THE TEXT

September 2019