1. NAME OF THE MEDICINAL PRODUCT

AFSTYLA 250IU powder and solvent for solution for injection
AFSTYLA 500IU powder and solvent for solution for injection
AFSTYLA 1000IU powder and solvent for solution for injection
AFSTYLA 1500IU powder and solvent for solution for injection
AFSTYLA 2000IU powder and solvent for solution for injection
AFSTYLA 2500IU powder and solvent for solution for injection
AFSTYLA 3000IU powder and solvent for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains nominally 250/500/1000/1500/2000/2500/3000 IU recombinant, single chain coagulation factor VIII (rVIII-SingleChain, INN = lonoctocog alfa).

After reconstitution with 2.5 mL water for injections (250/500/1000 IU) the solution contains 100/200/400 IU/mL of rVIII-SingleChain. When reconstituted with 5 mL water for injections (1500/2000/2500/3000 IU) the solution contains 300/400/500/600 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 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:
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.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

AFSTYLA is indicated in adults and pediatrics with hemophilia 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)

AFSTYLA is not indicated for treatment of Von Willebrand disease.

4.2 Posology and method of administration

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

The decision for an individual patient on the use of home treatment of bleeding and prophylaxis of bleeding in patients with hemophilia 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 milliliter 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. If using the one-stage clotting assay to monitor FVIII activity level, the one-stage assay results can be aligned to chromogenic substrate acquired results by multiplying the one-stage result by 2 (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
The safety and efficacy of AFSTYLA in previously untreated patients have not yet been established.

Pediatric population
In children the recommended starting regimen is 20-50 IU/kg of AFSTYLA administered 2 to 3 times a week. 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 pediatric 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.

Neutralizing antibodies
Formation of neutralizing 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. 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.

Patients should be monitored for the development of neutralizing 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 (neutralizing antibody) should be suspected.
A specialized hemophilia treatment center 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 hemostatic 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.

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.

Pediatric 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 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 fetal 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, generalized 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 trial of AFSTYLA (see below ADR table), no anaphylactic reactions were reported.

Patients with hemophilia A may develop neutralizing 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 specialized hemophilia center be contacted. No such reactions have been observed in completed clinical trials in previously treated patients with AFSTYLA.

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
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
Blood and lymphatic systems disorders*	Factor VIII inhibition	uncommon (PTPs) very common (PUPs)

*Inhibitor development has been observed in PUPs in an ongoing study and in postmarketing use.
In the ongoing 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.

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

Mechanism of Action
AFSTYLA (INN: lonoctocog alfa) is a recombinant protein that replaces the missing coagulation factor VIII needed for effective hemostasis. AFSTYLA 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 the AFSTYLA molecule formed 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 AFSTYLA to von Willebrand Factor.

Pharmacodynamic effects
Hemophilia 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.

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)
$AUC_{0\text{-}inf}$ (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; $AUC_{0\text{-}inf}$ = 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; V_{ss} = body weight adjusted volume of distribution at steady-state

Pediatric 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)
$AUC_{0\text{-}inf}$ (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 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

L-Histidine
Polysorbate 80
Calcium chloride di-hydrate
Sodium chloride
Sucrose

Hydrochloric acid (pH adjusting agent)

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

Do not store above +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. Do not return AFSTYLA to refrigeration after storage at room temperature.

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

6.5 Nature and contents of container

Immediate containers
Powder (250/500/1000/1500/2000/2500/3000 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 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
Administration set (inner box):
1 disposable 5 ml syringe
1 venipuncture set
2 alcohol swabs
1 non- sterile plaster

Box with 1500, 2000, 2500 or 3000 IU containing:
1 vial with powder
1 vial with 5 ml water for injections
1 filter transfer device 20/20
Administration set (inner box):
1 disposable 10 ml syringe
1 venipuncture set
2 alcohol swabs
1 non- sterile plaster

Not all pack sizes may be marketed.

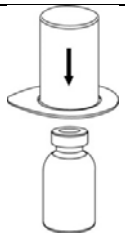
6.6 Precautions for disposal and other handling

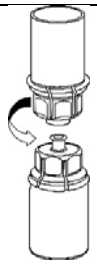
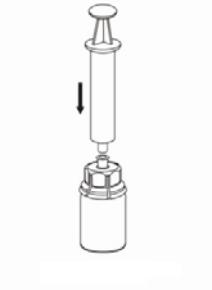
General instructions

- 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.

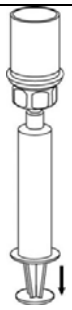
Reconstitution

Bring the Water for injection (WFI) to room temperature. Ensure AFSTYLA and Water for injection (WFI) 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 **Water for injection (WFI) 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 Water for injection (WFI) 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 Water for injection (WFI) vial with the Mix2Vial set attached and push the spike of the **transparent** adapter end **straight down** through the AFSTYLA vial stopper. The Water for injection (WFI) 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 Water for injection (WFI)-side and unscrew the set carefully counterclockwise into two pieces. Discard the Water for injection (WFI) 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

8. Date of Revision of The Text

October 2019