Product Information

AFSTYLA®

Australia

NAME OF THE MEDICINE

AFSTYLA® (recombinant, single chain coagulation factor VIII (rVIII-SingleChain); lonoctocog alfa (rch)), powder and solvent for solution for injection.

CAS registry number: 1388129-63-2

DESCRIPTION

AFSTYLA® is a single chain recombinant factor VIII (FVIII) produced in Chinese hamster ovary (CHO) cells. It is a construct where most of the B-domain occurring in wild-type, full-length FVIII and 4 amino acids of the adjacent acidic A3 domain were removed (amino acids 765 to 1652 of full-length FVIII).

The newly formed linkage of the heavy and light chain of FVIII introduces a new N-glycosylation site. As the furin cleavage site present in wild type FVIII between the B-domain and the A3 domain was removed, AFSTYLA® is expressed as a single chain FVIII molecule with covalent linkage between heavy and light chains; thereby keeping the molecule in the single chain form resulting in increased stability and increased von Willebrand Factor (VWF) affinity. The post-translational modifications are comparable to endogenous FVIII.

AFSTYLA® is purified by a controlled multi-step process including two virus reduction steps complementing each other in their mode of action.

No human or animal derived proteins are used in the purification or formulation processes of AFSTYLA®.

The potency in International Units (IU) is determined using the European Pharmacopoeia chromogenic assay calibrated against the current World Health Organisation (WHO) International Standard for FVIII concentrate. The specific activity of AFSTYLA® is 7400–16000 IU/mg protein.

AFSTYLA® is a preservative free, sterile, non-pyrogenic, lyophilised powder to be reconstituted with Water for Injections (WFI) for intravenous injection.

AFSTYLA® is a white or slightly yellow powder or friable mass. The solvent (WFI) is a clear colourless solution for reconstitution. One vial of AFSTYLA® contains nominally 250/500/1000/1500/2000/2500/3000 IU recombinant, single chain coagulation FVIII (rVIII-SingleChain, lonoctocog alfa).

After reconstitution with 2.5 mL Water for Injections (250/500/1000 IU) the solution contains 100/200/400 IU/mL of lonoctocog alfa. When reconstituted with 5 mL Water for Injections (1500/2000/2500/3000 IU) the solution contains 300/400/500/600 IU/mL of lonoctocog alfa.

Table 1: AFSTYLA® composition after reconstitution*

	250 IU	**500 IU**	**1000 IU**	**1500 IU**	**2000 IU**	**2500 IU**	**3000 IU**
Active ingredient (IU/mL)							
Factor VIII	100	200	400	300	400	500	600
Excipients (mg/mL)							
L-Histidine	3.1	3.1	3.1	3.1	3.1	3.1	3.1
Polysorbate 80	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Calcium chloride	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Sodium chloride	16.4	16.4	16.4	16.4	16.4	16.4	16.4
Sucrose	6	6	6	6	6	6	6
Reconstitution volume (mL)	**2.5**	**2.5**	**2.5**	**5**	**5**	**5**	**5**

* Nominal values

The sodium content is approximately 0.23–0.30 mmol/mL (5.4–7.0 mg/mL).

PHARMACOLOGY

Pharmacodynamics

Haemophilia A is an X-linked hereditary disorder of blood coagulation due to decreased levels of FVIII and results in profuse bleeding into joints, muscles or internal organs, either spontaneously or as a result of accidental or surgical trauma. By replacement therapy the plasma levels of FVIII are increased, thereby enabling a temporary correction of the factor deficiency and correction of the bleeding tendencies.

AFSTYLA® (lonoctocog alfa) is a recombinant protein that replaces the missing coagulation FVIII needed for effective haemostasis. AFSTYLA® is a single polypeptide chain with a

truncated B-domain that allows for a covalent bridge to link the FVIII heavy and light chains. Compared to full-length FVIII, the stabilised single-chain design results in increased binding affinity to VWF. VWF stabilises FVIII and protects it from degradation. Activated AFSTYLA® has an amino acid sequence identical to endogenous FVIIIa.

Pharmacokinetics

Adult population

The pharmacokinetics (PK) of AFSTYLA® were evaluated in 81 adults following an intravenous injection of a single dose of 50 IU/kg. The PK parameters (see **Table 2**) were based on plasma FVIII activity measured by the chromogenic 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.

Table 2: Pharmacokinetic parameters (arithmetic mean, CV%) following a single injection of 50 IU/kg of AFSTYLA® in 18 to 65 year old adults (chromogenic assay)

PK Parameters	rVIII-SingleChain 50 IU/kg (N = 81)
IR (IU/dL)/(IU/kg)	2.00 (20.8)
Cmax (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; Cmax = maximum concentration; $AUC_{0\text{-}inf}$ = area under the FVIII 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

Pharmacokinetics parameters of AFSTYLA® were evaluated in 49 previously treated subjects, 10 adolescents (≥12 to <18 years) and 39 children (0 to <12 years) in open-label, multicentre studies following a 50 IU/kg intravenous injection of AFSTYLA®. The PK parameters (see **Table 3**) were based on plasma FVIII activity measured by the chromogenic assay.

Table 3: 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)
Cmax (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; Cmax = maximum concentration; $AUC_{0\text{-}inf}$ = area under the FVIII 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.

CLINICAL TRIALS

The pharmacokinetics, safety and efficacy of AFSTYLA® were evaluated in two studies; a phase I/III study in adults/adolescents (Study 1001) as well as a phase III study in children (Study 3002). The studies characterised the PK of AFSTYLA® and determined haemostatic efficacy in the control of bleeding events, the prevention of bleeding events in prophylaxis and in the phase I/III adult/adolescent study determined haemostatic efficacy during perioperative management in subjects undergoing surgical procedures.

The adult/adolescent study enrolled a total of 175 previously treated male subjects with severe haemophilia A (<1% endogenous FVIII activity). Subjects ranged in age from 12 to 65 years, including 14 adolescent subjects (≥12 to <18 years). Of the 175 enrolled subjects, 174 received at least one dose of AFSTYLA® and 173 (99%) were evaluable for efficacy. A total of 161 subjects (92.5%) completed the study.

A total of 120 (69.0%) subjects were treated for at least 50 exposure days (EDs) and 52 (29.9%) of those subjects were treated for at least 100 EDs. Subjects received a total of 14,592 injections with a median of 67.0 (range 1 to 395 injections per subject).

The paediatric study enrolled 84 previously treated male subjects with severe haemophilia A (35 subjects 0 to <6 years and 49 subjects ≥6 to <12 years). Of the 84 enrolled subjects, all received at least 1 dose of AFSTYLA® and 83 (99%) were evaluable for efficacy. A total of 65 (77.4 %) subjects were treated for at least 50 EDs and 8 (9.5%) of those subjects were

treated for at least 100 EDs. Subjects received a total of 5,313 injections with a median of 59 (range 4 to 145 injections per subject).

Control and prevention of bleeding episodes

Adult and adolescent subjects (≥12 to 65 years of age)

In the adult/adolescent study a total of 848 bleeding episodes were treated with AFSTYLA® and 835 received an efficacy assessment by the investigator. The majority of the bleeding episodes were localised in joints.

The median dose per injection used to treat a bleeding episode was 31.7 IU/kg. Of these 848 bleeding episodes, 686 (81.0%) were controlled with a single AFSTYLA® injection and another 107 (13%) were controlled with 2 injections. Fifty-five (6%) of the 848 bleeding episodes required 3 or more injections.

For 94% of bleeding episodes the haemostatic efficacy rating evaluated by the investigator was either excellent or good.

Efficacy in control of bleeding episodes is summarised in **Table 4**.

Paediatric subjects (0 to <12 years of age)

In the paediatric study a total of 347 bleeding episodes were treated with AFSTYLA® all of which received an efficacy assessment by the investigator. The majority of the bleeding episodes were localised in joints.

The median dose per injection used to treat a bleeding episode was 27.3 IU/kg. Of the 347 bleeding episodes, 298 (86%) were controlled with a single AFSTYLA® injection and another 34 (10%) were controlled with 2 injections. Fifteen (4%) of the 347 bleeding episodes required 3 or more injections.

For 96% of bleeding episodes the haemostatic efficacy rating evaluated by the investigator was either excellent or good.

Efficacy in control of bleeding episodes is summarised in **Table 4**.

Table 4: Efficacy* of AFSTYLA® in control of bleeding

	Adult/Adolescent (Study 1001; ≥12 to 65 years of age)	Paediatric (Study 3002; 0 to <12 years of age)
Bleeding Episodes Treated	**(N = 848)**	**(N = 347)**
Number of injections		
1 injection, n (%)	686 (81%)	298 (86%)
2 injections, n (%)	107 (13%)	34 (10%)
3 injections, n (%)	29 (3%)	8 (2%)
>3 injections, n (%)	26 (3%)	7 (2%)
Efficacy evaluation by investigator*	**(N = 835)**	**(N = 347)**
Excellent or Good, n (%)	783 (94%)	334 (96%)
Moderate, n (%)	52 (6%)	12 (4%)
No response, n (%)	0	1 (0.3%)

* **Excellent**: Pain relief and/or improvement in signs of bleeding (i.e., swelling, tenderness, and/or increased range of motion in the case of musculoskeletal haemorrhage) within approximately 8 hours after the first infusion; **Good**: Pain relief and/or improvement in signs of bleeding at approximately 8 hours after the first infusion, but requires two infusions for complete resolution; **Moderate**: Probable or slight beneficial effect within approximately 8 hours after the first infusion; requires more than two infusions for complete resolution; **No response**: No improvement at all or condition worsens (i.e., signs of bleeding) after the first infusion and additional haemostatic intervention is required with another FVIII product, cryoprecipitate, or plasma for complete resolution.

Routine prophylaxis

In the adult/adolescent and paediatric studies, subjects received prophylaxis in a regimen that was determined by the investigator, taking into account the subject's FVIII treatment regimen used prior to enrollment and the subject's bleeding phenotype.

Adult and adolescent subjects (≥12 to 65 years of age)

In the adult/adolescent study 54% of the 146 subjects on prophylaxis received AFSTYLA® 3 times weekly; 32% of subjects received AFSTYLA® 2 times weekly; 6% received AFSTYLA® every other day, and 8% of subjects received other regimens.

Sixty-three of 146 subjects (43%) experienced no bleeding episodes requiring treatment while on prophylaxis. There were no severe or life-threatening bleeds (e.g. intracranial haemorrhage) in subjects receiving prophylaxis.

The median annualised bleeding rate (ABR) in prophylaxis was 1.14, a significantly lower ABR ($p < 0.0001$) than that observed in subjects treated on demand (median ABR 19.64).

The ABR was comparable between subjects on a 3 times a week regimen (median ABR 1.53) and those on a 2 times a week regimen (median ABR 0.00). The annualised spontaneous bleeding rate (AsBR) was identical between subjects on these regimens; a median AsBR of 0.00 on both a 3 times a week and on a 2 times a week regimen.

The median prescribed dose for subjects on a 3 times a week regimen was 30 IU/kg per injection, and for subjects on a 2 times a week regimen 35 IU/kg.

The ABRs for prophylaxis and on demand are summarised in **Table 5.**

Paediatric subjects (0 to <12 years of age)

In the paediatric study 54% of the 80 subjects on prophylaxis received AFSTYLA® 2 times weekly; 30% of subjects received AFSTYLA® 3 times weekly; 4% received AFSTYLA® every other day, and 12% of subjects received other regimens.

Twenty-one of 80 subjects (26%) experienced no bleeding episodes requiring treatment while on prophylaxis. There was one severe bleed (hip joint haemorrhage) in the paediatric study that was successfully treated.

For subjects on prophylaxis the overall ABR was 3.69, with a median ABR of 2.30 for subjects on a 3 times a week regimen and 4.37 for subjects on a 2 times a week regimen. The median AsBR (0.00) was identical between subjects on the 3 times a week and 2 times a week regimens.

The median prescribed dose for subjects on a 3 times a week regimen was 32 IU/kg per injection, and for subjects on a 2 times a week regimen 35 IU/kg.

The ABRs for prophylaxis and on demand are summarised in **Table 5.**

Table 5: Summary of annualised bleeding rate (ABR) by AFSTYLA® treatment regimen

	Adult/Adolescent (Study 1001; ≥ 12 to 65 years of age)		Paediatric (Study 3002; 0 to <12 years of age)	
	Prophylaxis (N = 146)	**On demand (N = 27)**	**Prophylaxis (N = 80)**	**On demand (N = 3)**
Overall ABR Median (IQR*)	1.14 (0–4.2)	19.64 (6.2–46.5)	3.69 (0–7.2)	78.56 (35.1–86.6)
Annualised Spontaneous Bleeding Rate (AsBR) Median (IQR*)	0 (0–2.4)	11.73 (2.8–36.5)	0 (0–2.2)	31.76 (0–42.7)
Number of subjects with zero bleeding episodes requiring treatment	63 (43.2%)	1 (3.7%)	21 (26.3%)	0

* IQR = interquartile range, 25th percentile to 75th percentile.

Control and prevention of bleeding episodes in the perioperative setting

Thirteen subjects in the adult/adolescent study underwent a total of 16 surgical procedures. Overall, investigators assessed haemostatic efficacy of AFSTYLA® in surgical prophylaxis as excellent in 15 of 16 surgeries and as good in 1 of 16 surgeries (see **Table 6**). Median factor consumption on the day of surgery was 89.4 IU/kg (range 40.5–108.6 IU/kg).

Table 6: Efficacy of AFSTYLA® in surgical prophylaxis

Procedure	Efficacy Evaluation*	Factor Consumption (IU/kg) (pre- and intra-operatively)
Extraction of wisdom teeth	Excellent	51.09
Abdominal hernia repair	Excellent	47.89
Elbow replacement	Excellent	108.58
Ankle arthroplasty	Excellent	76.83
Knee replacement (5)	Excellent (4), Good (1)	92.49 100.9 67.26 105.79 86.09
Cholecystectomy and Lengthening of the Achilles tendon combined with: Straightening of the right toes	Excellent Excellent	105.95
Circumcision (3)	Excellent (3)	99.04 92.74 81.5
Open reduction internal fixation (ORIF) right ankle	Excellent	89.36
Hardware removal, right ankle	Excellent	40.45

* **Excellent**: Haemostasis clinically not significantly different from normal (e.g., achieved haemostasis comparable to that expected during similar surgery in a non-factor deficient patient) in the absence of other haemostatic intervention and estimated blood loss during surgery is not more than 20% higher than the predicted blood loss for the intended surgery; **Good**: Normal or mildly abnormal haemostasis in terms of quantity and/or quality (e.g., slight oozing, prolonged time to haemostasis with somewhat increased bleeding compared to a non-factor deficient patient in the absence of other haemostatic intervention) or estimated blood loss is >20%, but ≤30% higher than the predicted blood loss for intended surgery; **Moderate**: Moderately abnormal haemostasis in terms of quantity and/or quality (e.g., moderate haemorrhage that is difficult to control) with estimated blood loss greater than what is defined as good; **Poor/No Response**: Severely abnormal haemostasis in terms of quantity and/or quality (e.g., severe haemorrhage that is difficult to control) and/or additional haemostatic intervention required with another FVIII product, cryoprecipitate, or plasma for complete resolution.

INDICATIONS

AFSTYLA® is indicated in adult and paediatric patients with haemophilia A (congenital FVIII deficiency) for:

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

AFSTYLA® is not indicated for the treatment of von Willebrand disease.

CONTRAINDICATIONS

AFSTYLA® is contraindicated in patients who have had life-threatening hypersensitivity reactions, including anaphylaxis, to AFSTYLA®, any of its components, or hamster proteins (see **Table 1**).

PRECAUTIONS

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.

Inhibitors

Formation of neutralising antibodies (inhibitors) to FVIII can occur following administration of FVIII products.

Patients should be monitored for the development of neutralising antibodies (inhibitors) by appropriate clinical observations and laboratory tests. If expected FVIII 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 FVIII 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

FVIII plasma activity in patients receiving AFSTYLA® can be monitored using either a chromogenic assay or a one-stage clotting assay. If available, the chromogenic assay should be used to determine FVIII activity in patient samples, as efficacy results of a large pivotal

clinical study confirmed that the chromogenic assay results most accurately reflect the clinical haemostatic potential.

Clinical trials have shown that the use of a one-stage assay produces results that are approximately 45% lower than those of the chromogenic assay. This should be taken into account when interpreting patient results if the one-stage method is used. One-stage assay results can be aligned to chromogenic assay results by multiplying the one-stage result by 2.

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.

Previously untreated patients

The safety and efficacy of AFSTYLA® in previously untreated patients (PUPs) have not yet been established.

Paediatric use

The listed precautions apply both to adults and children.

Effects on fertility

Animal reproduction studies have not been conducted with AFSTYLA®.

Use in pregnancy

Category B2

No developmental or animal reproduction toxicity studies were conducted with AFSTYLA®. Thus, the risk of developmental toxicity including, structural abnormalities, embryo-fetal and/or infant mortality, functional impairment, and alterations to growth cannot be evaluated. AFSTYLA® should be given to a pregnant woman only if clearly needed.

Use in lactation

No animal studies were performed investigating the excretion of AFSTYLA® into milk or its effect on lactation and breast-feeding infants. Use AFSTYLA® only if clearly needed when treating a breast-feeding woman.

Genotoxicity

Genotoxicity studies have not been conducted with AFSTYLA®.

Carcinogenicity

Carcinogenicity studies have not been conducted with AFSTYLA®.

INTERACTIONS WITH OTHER MEDICINES

Studies investigating drug-drug interactions have not been conducted with AFSTYLA®. No interactions of AFSTYLA® with other medicinal products have been reported.

ADVERSE EFFECTS

Summary of the safety profile

In the completed adult/adolescent study (Study 1001; ≥12 to 65 years of age), the 174 subjects treated had a mean (SD) of 82.2 (61.35) exposure days (EDs) and a mean (SD) study duration of 258.8 (163.52) days (i.e. 8.5 months) and 52 (29.9%) subjects achieved at least 100 EDs.

In the completed paediatric study (Study 3002; 0 to <12 years of age), the 84 subjects treated had a mean (SD) of 62.4 (24.73) EDs and a mean (SD) study duration of 183.5 (61.16) days (i.e. 6.0 months). There were 65 (77.4%) subjects who had achieved at least 50 EDs and 8 (9.5%) subjects who had achieved at least 100 EDs.

In the ongoing extension study (Study 3001), 154 subjects had a mean (SD) of 145.2 (68.69) EDs counted from the first day of exposure to rVIII-SingleChain in the pivotal studies. A total of 152 (98.7%) subjects had achieved at least 50 EDs, of whom 109 (70.8%) had achieved at least 100 EDs (counted from the first day of exposure to rVIII-SingleChain in the pivotal studies).

During completed clinical trials with AFSTYLA® conducted in 258 adult and paediatric previously treated patients, there were 475 adverse events reported in 177/258 (68.6%) subjects who received a total of 19,905 injections. Of these 475 events, 20 (4.2%) were reported as related to AFSTYLA® in 14/258 (5.4%) subjects.

Tabulated list of adverse reactions

Table 7 is presented according to the MedDRA system organ classification (SOC and preferred term level).

Table 7: Frequency of adverse reactions observed in clinical studies

MedDRA System Organ Class	MedDRA Preferred Term	Frequency category acc to CIOMS*
Immune system disorders	Hypersensitivity	common
Nervous system disorders	Dizziness Paraesthesia	common common
Skin and subcutaneous tissue disorders	Rash Erythema Pruritus	common uncommon uncommon
General disorders and administration site conditions	Pyrexia Injection site pain Chills Feeling hot	common uncommon uncommon uncommon

* Frequencies have been evaluated on a per patient basis 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).

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 with the use of FVIII products and may in some cases progress to severe anaphylaxis (including shock) (see also **PRECAUTIONS**). Hypersensitivity reactions were observed in clinical trials of AFSTYLA® (see **Table 7**), no anaphylactic reactions were reported.

Patients with haemophilia A may develop neutralising antibodies (inhibitors) to FVIII. 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 identified in previously treated patients in completed clinical studies for AFSTYLA®. Inhibitor development has been observed in PUPs in an ongoing study. There is insufficient data to provide information on inhibitor incidence in PUPs.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation 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.

DOSAGE AND ADMINISTRATION

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

It is recommended that prescribed doses of AFSTYLA® are expressed as 'International Units' written in full.

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.

Dosage

The dose and duration of the treatment depend on the severity of the FVIII deficiency, the location and extent of the bleeding, and the patient's clinical condition.

The number of units of FVIII administered is expressed in International Units (IU), which are related to the current WHO standard for FVIII products. FVIII activity in plasma is expressed either as a percentage (relative to normal human plasma) or in IU (relative to an International Standard for FVIII in plasma).

Each vial label of AFSTYLA® states the FVIII potency in IU. One IU corresponds to the activity of FVIII contained in one millilitre of normal human plasma.

Potency assignment is determined using a chromogenic assay. Plasma FVIII levels can be monitored using either a chromogenic assay or a one-stage clotting assay (see **PRECAUTIONS**). The chromogenic assay results most accurately reflect the clinical haemostatic potential. If using the one-stage assay to monitor FVIII activity level, the results can be aligned to chromogenic assay acquired results by multiplying the one-stage result by 2.

On demand treatment

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

Estimated Increment of FVIII (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 FVIII level may be calculated using the following formula:

Dose (IU) = body weight (kg) x Desired FVIII 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 **Table 8**. Consideration should be given to maintaining a FVIII activity at or above the target range.

Table 8: Dosing for control and prevention of bleeding episodes and in the perioperative setting

Degree of haemorrhage	FVIII level required (% or IU/dL)	Dose (IU/kg)	Frequency of Doses (hours)
Early haemarthrosis muscle bleeding or oral bleeding	20–40	10–20	Repeat injection every 12–24 hours until the bleeding is resolved.
More extensive haemarthrosis muscle bleeding or haematoma	30–60	15–30	Repeat injection every 12–24 hours until the bleeding is resolved.
Life-threatening haemorrhages	60–100	30–50	Repeat injection every 8–24 hours until bleed is resolved.
Control and prevention of bleeding in the perioperative setting	**FVIII level required (% or IU/dL)**	**Dose (IU/kg)**	**Frequency of doses (hours)/Duration of therapy (days)**
Minor surgery (including tooth extraction)	30–60	15–30	Repeat injection every 24 hours for at least 1 day, until healing is achieved.
Major surgery	80–100 (pre- and postoperative)	40–50	Repeat injection every 8–24 hours until adequate wound healing, then continue therapy for at least another 7 days to maintain a FVIII 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.

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).

Older people

Clinical studies of AFSTYLA® did not include patients aged over 65 years.

Monitoring advice

Patients should be monitored to confirm adequate FVIII levels have been achieved and maintained, and for the development of FVIII inhibitors. See **PRECAUTIONS**.

General instructions

For intravenous use only after reconstitution.

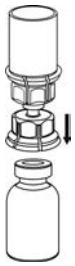
The solution should be almost colourless, clear or slightly opalescent. After filtering/withdrawal (see **Reconstitution**) the reconstituted product should be inspected visually for particulate matter and discoloration prior to administration.

Do not use visibly cloudy solutions or solutions still containing flakes or particles.

Reconstitution and withdrawal must be carried out under aseptic conditions.

Reconstitution

 1	1. Bring the WFI to room temperature. Ensure AFSTYLA® and 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. Open the Mix2Vial™ package by peeling off the lid. Do **not** remove the Mix2Vial™ from the blister package!
 2	2. Place the **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 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 WFI vial with the Mix2Vial™ set attached and push the spike of the **transparent** adapter end **straight down** through the AFSTYLA® vial stopper. The 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 WFI side and unscrew the set carefully counterclockwise into two pieces. Discard the 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 FVIII adsorption to the internal surface of some injection equipment.

Care should be taken that no blood enters the syringe filled with AFSTYLA®, 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.

Administration

Intravenous use.

For instructions on reconstitution of the medicinal product before administration, see **General instructions**. The reconstituted preparation should be injected slowly intravenously 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 **PRECAUTIONS**.

Use in one patient on one occasion only.

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

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.

Compatibility with other medicines

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 **DESCRIPTION**.

OVERDOSAGE

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.

For general advice on overdose management, contact the Poisons Information Centre on 131 126.

PRESENTATION AND STORAGE CONDITIONS

Store at 2°C to 8°C. Refrigerate (Do not freeze).

AFSTYLA® may be stored at room temperature (up to 25°C) for a single period of up to 3 months and then discarded. Do not return AFSTYLA® to refrigeration after storage at room temperature.

Do not use AFSTYLA® after the expiry date.

Keep vials in the outer carton in order to protect from light.

AFSTYLA® should be used as soon as possible after reconstitution and within 4 hours at or below 25°C.

Presentation

AFSTYLA® is available in the following presentations:

- Powder (250/500/1000 IU) in a 5 mL vial (type I glass), with a stopper (rubber) a disc (plastic) and a cap (aluminium)

  2.5 mL of Water for Injections in a vial (type I glass), with a stopper (rubber) a disc (plastic) and a cap (aluminium)

- Powder (1500/2000/2500/3000 IU) in a 10 mL vial (type I glass), with a stopper (rubber) a disc (plastic) and a cap (aluminium)

  5 mL of Water for Injections in a vial (type I glass), with a stopper (rubber) a disc (plastic) and a cap (aluminium).

AFSTYLA® is supplied as:

One pack with 250, 500 or 1000 IU containing:

1 vial with powder
1 vial with 2.5 mL Water for Injections
One administration pack containing:
1 filter transfer set 20/20
1 syringe (5 mL)
1 venipuncture set (butterfly)
2 alcohol swabs
1 plaster (not sterile)

One pack with 1500, 2000, 2500 or 3000 IU containing:

1 vial with powder
1 vial with 5 mL Water for Injections
One administration pack containing:
1 filter transfer set 20/20
1 syringe (10 mL)
1 venipuncture set (butterfly)
2 alcohol swabs
1 plaster (not sterile)

Not all pack sizes may be marketed.

NAME AND ADDRESS OF THE SPONSOR AND DISTRIBUTOR

CSL Behring (Australia) Pty Ltd
ABN 48 160 734 761
189–209 Camp Road
Broadmeadows VIC 3047
Australia

POISON SCHEDULE OF THE MEDICINE (Australia)

Unscheduled

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

13 April 2017

DATE OF MOST RECENT AMENDMENT

Not applicable

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