Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for lonoctocog alfa (rch)

Proprietary Product Name: Afstyla

Sponsor: CSL Behring Australia Pty Ltd

January 2018

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

Abbreviation	Meaning
ABR	Annualised bleeding rate
ACM	Advisory Committee on Medicines
ADA	Anti-drug antibody
AE	Adverse event
aPTT	Activated partial thromboplastin time
ARTG	Australian Register of Therapeutic Goods
ASA	Australian Specific Annex
AsBR	Annualised spontaneous bleeding rate
AUC	Area under the curve
$AUC_{0-\infty}$	Area under the curve from time zero to infinity
BLA	Biological License Application
BP	Blood pressure
BU	Bethesda unit
CER	Clinical evaluation report
CHO	Chinese hamster ovary
ChS	Chromogenic substrate
C_{max}	Maximal plasma concentration
CMI	Consumer Medicines Information
CNS	Central nervous system
CTD	Common Technical Document
DLP	Data lock point
ECG	Electrocardiogram
ED	Exposure day
EMA	European Medicines Agency
EU	European Union

Abbreviation	Meaning
EUHASS	European Haemophilia Safety Surveillance system
FDA	Food and Drug Administration
FVIII	(Coagulation) Factor VIII
GLP	Good Laboratory Practice
ICH	International Conference on Harmonisation
ITT	Intention to treat
IU	International Units
IV	Intravenous
kDa	Kilodalton
LFT	Liver function test
LLOQ	Lower limit of quantification
MW	Molecular weight
OS	One stage
Ph. Eur	European Pharmacopoeia
PI	Product Information
PK	Pharmacokinetic
PP	Per protocol
PSUR	Periodic Safety Update Report
PUP	Previously untreated patient
rDNA	Recombinant DNA
rFVIII	Recombinant human coagulation Factor VIII
rFVIIIa	Activated rFVIII
RMP	Risk Management Plan
RP-HPLC	Reversed phase high performance liquid chromatography
SAE	Serious adverse event
SE-HPLC	Size exclusion high performance liquid chromatography

Abbreviation	Meaning
SmPC	Summary of Product Characteristics
$t_{1/2}$	Half life
TEAE	Treatment emergent adverse event
WFH	World Federation on Hemophilia
WFI	Water for injection
US	United States

I. Introduction to product submission

Submission details

Type of submission:	New biological entity
Decision:	Approved
Date of decision:	29 March 2017
Date of entry onto ARTG	13 April 2017
Active ingredient:	Lonoctocog alfa (rch)
Product name:	Afstyla
Sponsor's name and address:	CSL Behring Australia Pty Ltd 189-209 Camp Road, Broadmeadows, VIC, 3047
Dose form:	Powder for injection
Strengths:	250 IU, 500 IU, 1000 IU, 1500 IU, 2000 IU, 2500 IU, and 3000 IU
Container:	Vial (glass type I clear)
Pack sizes:	1 x single use composite pack containing: 1 x vial (glass type I clear) containing 250 IU, 500 IU, 1000 IU, 1500 IU, 2000 IU, 2500 IU, or 3000 IU Afstyla, powder for injection 1 x vial (glass type I clear) containing 2.5 mL Water for Injections (250 IU, 500 IU, and 1000 IU strengths only); or 5.0 mL Water for Injections (1500 IU, 2000 IU, 2500 IU or 3000 IU strengths only) 1 x Mix2Vial (and administration pack) polycarbonate transfer device
Approved therapeutic use:	*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.*
Route of administration:	Intravenous
Dosage:	Different dosage regimens exist for on demand and prophylactic treatment. See the relevant descriptions of these dosage regiments below in conjunction with the approved Product Information (see Attachment 1) for further details.
ARTG numbers:	270335, 271633, 271634, 271635, 271636, 271637, 271638

Product background

This AusPAR describes the application by the sponsor to register Afstyla lonoctocog alfa (rch) powder (and solvent) for injection, as a new biological entity for the following indication:

> *'Afstyla is indicated in all 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).'*

Lonoctocog alfa is a form of recombinant coagulation factor VIII (rFVIII). It differs from endogenous factor VIII (FVIII) in that a segment of the molecule (most of the B-domain and 4 amino acids of the adjacent *a3* domain) has been removed. It is produced in Chinese hamster ovary (CHO) cells.

The proposed product is a lyophilised powder, to be reconstituted with water for injections (WFI) for intravenous injection. 7 strengths are proposed: 250, 500, 1000, 1500, 2000, 2500 and 3000 International Units (IU).

The initial submission to the TGA included an additional dose form of 375 IU. On 10 November 2016, the sponsor informed the TGA that they do not wish to pursue registration of the 375 IU presentation of Afstyla. This presentation is not registered in the US and has been removed from the Afstyla application in the EU.

The proposed dosage varies according to the clinical scenario. Dosages for the treatment of haemorrhage and use in surgery are calculated using the following formula:

> Dose (IU) = body weight (kg) x desired FVIII rise (as IU/dL or % of normal) x 0.5 (IU/kg per IU/dL).

Recommended doses for haemorrhage and in the surgical setting are summarised below in Table 1 taken from the draft Product Information (PI). The proposed prophylaxis starting regimen is 20 to 50 IU/kg of Afstyla administered 2 to 3 times weekly.

Table 1. Proposed recommended dose according to clinical indication

Degree of haemorrhage	**FVIII level required (% or IU/dL)**	**Frequency of Doses (hours)**
Early haemarthrosis muscle bleeding or oral bleeding	20–40	Repeat injection every 12–24 hours until the bleeding is resolved.
More extensive haemarthrosis muscle bleeding or haematoma	30–60	Repeat injection every 12–24 hours until the bleeding is resolved.
Life-threatening haemorrhages	60–100	Repeat injection every 8–24 hours until bleed is resolved.
Control and prevention of bleeding in the perioperative setting	**FVIII level required (% (IU/dL)**	**Frequency of doses (hours)/Duration of therapy (days)**
Minor surgery e.g. (including tooth extraction)	30–60	Repeat injection every 24 hours for at least 1 day, until healing is achieved.
Major surgery	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 FVIII activity of 30–60% (IU/dL).

Haemophilia A

Congenital haemophilia A is a hereditary disorder caused by deficiency or dysfunction of coagulation Factor VIII (FVIII). The gene for FVIII is located on the X chromosome, and the disorder is inherited as an X-linked recessive condition. Therefore, most subjects with haemophilia A are males.[1]

The clinical manifestations of haemophilia are due to haemorrhage. The disorder can be classified as mild (plasma FVIII levels 5 to < 40% of normal), moderate (1 to 5% of normal) and severe (< 1% of normal).[2] Subjects with severe haemophilia A suffer from recurrent spontaneous bleeding, typically into joints and muscles. Repeated haemorrhages into joints can result in a chronic arthropathy.[3]

The 2013 to 2014 Annual Report of the Australian Bleeding Disorders Registry estimated that there were 2,181 subjects in Australia with haemophilia A.[4]

Recombinant human coagulation factor eight (rFVIII) is a mainstay in the prevention and treatment of bleeding in patients with haemophilia A.

Treatment of haemophilia A is based on the use of replacement FVIII products. Replacement therapy may be 'on demand' where treatment is given when a haemorrhage occurs, or prophylactic FVIII is administered at regular intervals in an attempt to prevent the onset of haemorrhage. FVIII replacement products currently registered in Australia are summarised below in Table 2.

Endogenous FVIII circulates in plasma as a molecule with 2 chains connected by a disulphide bond: a heavy chain at the NH_2 end (molecular weight (MW) around 90 to 200 kilodaltons (kDa)) and a light chain at the COOH end (MW around 80 kDa). The molecule is also organised into a series of domains which are labelled (from the NH_2 terminal end) as A1, *a1*, A2, *a2*, B, *a3*, A3, C1 and C2. The *a1*, *a2*, and *a3* domains are short spacers domains and are referred to as the acidic regions.[5]

Table 2. Factor VIII replacement products currently registered in Australia

AAN	Tradename	Indication	Sponsor
Recombinant products			
Octocog alfa (rch)	Advate	For use in haemophilia A for prevention and control of haemorrhagic episodes. Patients with haemophilia A may be treated with Advate as perioperative management. Advate is not indicated in von Willebrand's disease.	Baxalta

[1] Mannucci, P and Tuddenham, E. The hemophilias-from royal genes to gene therapy (2001). N Engl J Med, 344 (23): 1773-9.
[2] World Federation of Hemophilia. Guidelines for the Management of Hemophilia (2nd edition) (2002).
[3] Peyvandi F. The past and future of haemophilia: diagnosis, treatments, and its complications (2016). The Lancet, Published online: February 2017.
[4] National Blood Authority Australia. (n.d.). Australian Bleeding Disorders Registry. Annual Report 2013-2014.
[5] Lenting, P et al. The Life Cycle of Coagulation Factor VIII in View of Its Structure and Function (1998). Blood, 92 (11): 3983-3996.

AAN	Tradename	Indication	Sponsor
Octocog alfa (bhk)	Kogenate FS	For the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital Factor VIII deficiency). It may also be used in patients with Factor VIII inhibitors (neutralising antibodies) who continue to respond to infused Factor VIII. Kogenate FS does not contain von Willebrand Factor and hence is not indicated in von Willebrand's disease.	CSL Behring
Octocog alfa (bhk)	Kovaltry	Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). Kovaltry can be used for all age groups. (See Clinical Trials section). Kovaltry does not contain von Willebrand factor and is not indicated in von Willebrand disease.	Bayer
Octocog alfa (rch)	Recombinate	For use in haemophilia A (classical haemophilia) for the prevention and control of haemorrhagic episodes. Patients with haemophilia A may be treated with Recombinate as perioperative management. Recombinate is not indicated in von Willebrand's disease.	Baxalta
Moroctocog alfa	Xyntha	For the control and prevention of haemorrhagic episodes in patients with haemophilia A, including control and prevention of bleeding in surgical settings. Xyntha does not contain von Willebrand factor and should not be used by patients with von Willebrand's disease.	Pfizer
Turoctocog alfa	NovoEight	For the treatment and prophylaxis of bleeding episodes in patients with haemophilia A, including control and prevention of bleeding in surgical settings.	Novo Nordisk
Simoctocog alfa	Nuwiq	Treatment and prophylaxis of bleeding (also during and after surgery) in previously treated paediatric (> 2 years) and adult patients with haemophilia A (congenital factor VIII deficiency). Nuwiq does not contain von Willebrand Factor and is thus not indicated to treat von Willebrand's Disease.	Octapharma

AAN	Tradename	Indication	Sponsor
Susoctocog alfa	Obizur	Obizur, Anti haemophilic Factor (Recombinant), Porcine Sequence, is a recombinant DNA derived, anti-haemophilic factor indicated for the treatment of bleeding episodes in adults with acquired haemophilia A. Safety and efficacy of Obizur have not been established in patients with baseline anti-porcine factor VIII inhibitor titre greater than 20 BU. Obizur is not indicated for the treatment of congenital haemophilia A or von Willebrand disease.	Baxalta
Plasma derived products			
Human coagulation factor VIII and von Willebrand factor	Biostate	The prophylaxis and treatment of non-surgical and surgical bleeding associated with FVIII deficiency due to haemophilia A. The prophylaxis and treatment of non-surgical and surgical bleeding in patients with von Willebrand disease when desmopressin (DDAVP) treatment is ineffective or contraindicated.	CSL Behring
Human coagulation factor VIII and von Willebrand factor	Wilate	Von Willebrand disease (VWD): treatment of bleeding episodes including surgical bleeding in patients with von Willebrand's disease when desmopressin treatment is effective or contraindicated. Haemophilia A: treatment and prophylaxis of bleeding including surgical bleeding in patients with haemophilia A (congenital FVIII deficiency). There are insufficient data to recommend the use of Wilate in children less than 12 years of age	Octapharma
Human coagulation factor VIII	Octanate	Treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). This preparation does not contain von Willebrand factor in pharmacologically effective quantities and is therefore not indicated in von Willebrand's disease.	Octapharma

Lonoctocog alfa

In the lonoctocog alfa molecule, most of the B-domain and 4 amino acids of the adjacent *a3* region have been removed (amino acids 765 to 1652 of full length FVIII). The cleavage site present in wild type FVIII between the heavy and light chains (that is, between the B-domain and the *a3* region) is also removed, and therefore lonoctocog is expressed as a single chain FVIII molecule. The new linkage of the heavy and light chains of FVIII also

introduces a new N-glycosylation site. The lonoctocog molecule contains 1444 amino acids and has a molecular weight of approximately 170 kDa.

According to the sponsor these modifications were made in order to:

- Avoid potential dissociation of the heavy and light chains of non-activated FVIII;
- Reduce the chance of potential neoantigenicity by making use of the shielding effect of the new N-glycan side chain formed at the linkage site;
- Achieve high expression yield of rFVIII; and
- Obtain high process yield due to the stable single chain rFVIII construct.

In the submission documentation, the sponsor generally referred to the product as 'rVIII-SingleChain'. For consistency, this term will also be used in this overview document.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 13 April 2017

At the time the TGA considered this application, similar applications had been approved in the European Union (EU), United States (US) and Canada as shown below in Table 3.

Table 3. Foreign regulatory status

Country/Region	Status	Indication
United States (US)	Approved on 25 May 2016	Afstyla, Antihemophilic Factor (Recombinant), Single Chain, is a recombinant, antihemophilic factor indicated in adults and children with hemophilia A (congenital Factor VIII deficiency) for: 1. On-demand treatment and control of bleeding episodes, 2. Routine prophylaxis to reduce the frequency of bleeding episodes, 3. Perioperative management of bleeding.
Canada	Approved on 12 December 2016	Afstyla (Antihemophilic Factor VIII (Recombinant), SingleChain) is a recombinant DNA-derived, antihemophilic factor indicated in adults and children with hemophilia A (congenital Factor VIII deficiency) for: 1. Control and prevention of bleeding episodes 2. Routine prophylaxis to prevent or reduce the frequency of bleeding episodes, 3. Perioperative management of

Country/Region	Status	Indication
		bleeding (surgical prophylaxis).
European Union (EU) (Centralised procedure	Approved on 4 January 2017	[For the] treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency). Afstyla can be used for all age groups

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

Table 4. Registration timeline for Afstyla PM-2015-04357-1-4

Description	Date
Submission dossier accepted and 1st round evaluation commenced	29 February 2016
1st round evaluation completed	4 August 2016
Sponsor provides responses on questions raised in 1st round evaluation	5 October 2016
2nd round evaluation completed	7 November 2016
Delegate's overall risk-benefit assessment and request for Advisory Committee advice	3 January 2017
Sponsor's pre-Advisory Committee meeting response	17 January 2017
Advisory Committee meeting	3 February 2017
Registration decision	29 March 2017
Entry onto ARTG	13 April 2017
Number of TGA working days from submission dossier acceptance to registration decision *	228 days

* Target timeframe for standard applications: 220 working days

III. Quality findings

Drug substance (active ingredient)

Lonoctocog alfa is a single chain recombinant FVIII construct where most of the B-domain occurring in wild type, full length FVIII and 4 amino acids of the adjacent acidic *a3* domain have been removed (amino acids 765 to 1652 of full length FVIII). It has 1444 amino acids in a single chain glycopeptide with a molecular weight of approximately 170 kDa.

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, rVIII-SingleChain is expressed as a single chain FVIII molecule. This concept was developed to avoid potential dissociation of heavy and light chain of non-activated FVIII, and to achieve both higher expression yields of rVIII-SingleChain and higher process yields due to the stable one chain rVIII-SingleChain construct. The sponsor has stated the potential shielding effect of the newly generated N-glycanside chain formed at the linkage site may reduce the chance of neoantigenicity.

After activation by thrombin and removal of the (residual) B- and *a3*-domain, the activated rFVIII (rFVIIIa) molecule formed has an amino acid sequence identical to FVIIIa formed from endogenous, full length, FVIII.

Drug substance production

Starting from the rVIII-SingleChain working cell bank vial from CHO cells, the working cell bank vial undergoes thawing and expansion in shake flasks, followed by expansion in disposable rocking back bioreactors and the commercial scale bioreactor before harvest collection to produce the bulk harvest drug product.

The bulk harvest is purified using several chromatography steps and two virus inactivation/reduction steps.

Throughout the various steps of drug substance production outlined above, the drug product material undergoes in process control testing and in process acceptance criteria testing. All manufacturing steps and analytical procedures are validated.

Stability

Bulk drug intermediate

Stability data were generated under real time conditions to characterise the stability profile of the substance and to establish a shelf life. Further data was provided as part of a response to further TGA questions justifying a longer bulk drug intermediate shelf life

Drug substance

Further data was provided as part of a response to TGA questions justifying a longer drug substance shelf life. This is supported by the evaluator.

Drug product

All drug product manufacturing steps and analytical procedures are validated.

The evaluator recommends that prior to registration, the sponsor should be required to tighten the drug product specifications for the excipients histidine and polysorbate 80 to 80 to 120% of the stated potency as per European Pharmacopoeia (Ph. Eur) 01/2008:1643 Human coagulation factor VIII (recombinant DNA (rDNA)) requirements.

In the sponsor's response, they have stated that they acknowledge the specifications for the excipients histidine and polysorbate 80 exceed the compendial requirements and the sponsor agrees to tighten these specifications, as requested, in accordance with the Ph. Eur 01/2008:1643 Human coagulation factor VIII (rDNA) requirements. The adjusted specification ranges have been updated in the relevant Common Technical Document (CTD) sections.

The new specifications submitted still do not meet the Ph. Eur requirement to be 80% to 120% of the stated content.

The drug product FVIII 375 IU presentation has been withdrawn.

Stability

Stability data have been generated under stressed, real time and cycling conditions to characterise the stability profile of the product. In-use stability data have also been submitted. Stability studies have been conducted in accordance with relevant International Conference on Harmonisation (ICH) guidelines. Photostability data demonstrate the product is not photostable.

The proposed shelf life is:

- 36 months at +5°C
- including 3 months storage at ≤ 25°C for a single period during the 36 month time period, for all dosage strengths
- protected from light
- reconstituted product: 4 hours ≤ 25°C

The accelerated and temperature shift data does support the product stored for a single period of up to 3 months at ≤ 25°C within the expiration date. However, based on the cycling data presented, the product should not be returned to storage for the remainder of the shelf life (2 to 8°C).

This is also in line with the approved FDA storage conditions where they have placed the requirement for batches to not be returned to refrigeration after storage at 3 months at 25°C.

In conclusion, the evaluator cannot recommend approval for the proposed shelf life. The recommended shelf life for the drug product should be set as follows:

- 36 months at 2 to 8°C
- The product may be stored for a single period of 3 months at ≤ 25°C. If stored at ≤ 25°C the product should not be refrigerated again and should expire after 3 months, or after the expiration date on the product vial, whichever is earlier
- protected from light
- reconstituted product: 4 hours ≤ 25°C

As a result of the quality evaluator conclusions, the sponsor presented the following response:

> *'The sponsor has not requested specific temperature excursions during shipping. Therefore, post-approval, Afstyla drug product batches exposed to any temperature excursions outside the proposed storage conditions above should not be supplied, and should be quarantined until a subsequent application to vary has been determined by the TGA.*

The sponsor accepts the TGA recommended shelf life conditions for drug product. The storage conditions have been updated in the PI and Consumer Medicine Information (CMI) with wording that aligns with the TGA recommendations.

The sponsor acknowledges that with the existing data, the proposed storage condition of 3 months at ≤ 25°C cannot be used to support temperature excursions during transport as any excursion temperature and time would need to be added to the shelf life as stated by TGA. The sponsor would like to, however, refer the TGA to data to support a specific temperature excursion during transport:

A stability study was submitted with the original application which had a modified schedule, including pre-storage at +25°C for 3 weeks prior to commencing the stability program of 3 months at +25°C and 33 months at +5°C (Study 808-016). As this study covers a total testing period of 36 months + 3 weeks (Afstyla proposed shelf life 36 months), with 3 months and 3 weeks at +25°C, it is supportive of temperature excursions that may occur on transport. Data from this study is available for 24 months ([the relevant section] has been updated with additional stability data) and results are within specification and do not show any significant trends.

[The sponsor] has also commenced a transport excursion study, which includes storage at +40°C for 1 week, in addition to the proposed shelf-life conditions of 3 months at +25°C and 33 months at +5°C. The stressed storage condition of +40°C at 1 week was introduced to represent a worst case scenario for a temperature excursion during transport. Data from this study is available for 3 months across all strengths (refer to attachment); results are within specification and are comparable to results from samples not exposed to +40°C.

In addition to the above data sets, [the sponsor] would also like to highlight that the company has been shipping clinical and commercial batches of recombinant products (rFVII-FP, Idelvion and Afstyla) between Europe, USA, Asia and Australia for many years and the practical data from that experience shows that the majority of temperature excursions experienced have been in a range of up to +25°C for ≤ 18 hours. Therefore, to address TGAs concern, [the sponsor] proposes an allowance for a temperature excursion during transport of up to +25°C for ≤ 18 hours, which is an appropriate practical approach and is sufficiently supported by the stability data referenced above.

To further support this proposal, [the sponsor] commits to supplying the TGA with results from the ongoing Study 808-016 and the transport excursion study at the next available stability time points.

The amended shelf life conditions, and subsequent wording provided, are in line with TGA recommendations above. This is supported by the evaluator.

With regards to the proposed temperature excursion during transport, the data referred to (Study 808-016) does not appear to be from the original submission as stated. This study is included in subsequent [submitted data]. Furthermore, the proposed allowable temperature excursion for transport of 18 hours at ≤ 25°C is not supported by the data provided. The data (including the recently commenced study) does support an excursion of ≤ 25°C for 18 hours followed by 3 months at +25°C, however when the stability batches are returned to +2 to 8°C significant downward trends are observed for potency as discussed previously. To support the proposed excursion, the TGA would require stability data demonstrating when the drug product is exposed to +25°C for 18 hours and returned immediately to 2 to 8°C, the downward trends for potency are markedly reduced throughout the shelf life of 36 months.

Therefore, the evaluator cannot recommend approval of the proposed temperature excursion for transport of 18 hours at ≤ 25°C.

Extreme conditions of the 5 stress modes photolysis, temperature, chemical oxidation, acidity and alkalinity as well as shear force, to a greater or lesser extent, caused decreases in FVIII activity (potency) and in the purity of rVIII-SingleChain as measured by reversed phase high performance liquid chromatography (RP-HPLC) or size exclusion high performance liquid chromatography (SE-HPLC). Low pH, high temperature and photolysis conditions caused aggregation as detected by SE-HPLC. The following assays included in the current drug substance and/or drug product specification were able to identify the degradation of rVIII-SingleChain, confirming the stability-indicating potential of these assays for monitoring ongoing stability studies:

- chromogenic substrate FVIII activity assay (ChS FVIII activity)
- size-exclusion high performance liquid chromatography (SE-HPLC)
- Reversed-phase high performance liquid chromatography (RP-HPLC)

The degradation pathways were further investigated by the sponsor using additional assays including Liquid chromatography–mass spectrometry (LC-MS). Besides aggregation other mechanisms of degradation are oxidation of methionine residues and under certain conditions deamidation of asparagine residues.

Biopharmaceutics

Bioavailability/bioequivalence data were not required.

Quality summary and conclusions

Considerations for the delegate

There are objections on quality grounds to the approval of Afstyla lonoctocog alfa (rch) unless the issues below are resolved.

Summary of issues

Drug product excipients

- The new specifications submitted still do not meet the Ph. Eur requirement to be 80% to 120% of the stated content. The sponsor should be asked to further amend these specifications as agreed.

Drug product stability

The sponsor has agreed to change their shelf life conditions to:

- 36 months at 2 to 8°C
- The product may be stored for a single period of 3 months at ≤ 25°C. If stored at ≤ 25°C the product should not be refrigerated again and should expire after 3 months, or after the expiration date on the product vial, whichever is earlier.

However, as part of the sponsor's response, the sponsor requested a temperature excursion during shipping of ≤ 18 hours at ≤ 25°C. It is stated that a stability study provided in the original submission (Study 808-016: 3 months and 3 weeks at +25°C followed by 36 months at 2 to 8°C) supports this, as well as a new study (40°C for 1 week, followed by 3 months at +25 °C and 33 months at 2 to 8°C). However, Study 808-016 cannot be located in the original submission as stated. Furthermore, neither study supports the proposed temperature excursion of ≤ 18 hours at ≤ 25°C for the following reason:

- Stability data previously evaluated shows that when subjected to +25°C for 3 months and returned to 2 to 8°C there is a significant downward trend in potency so that if product was released at the lower end of release specification (90% of stated potency), the product will not meet end of shelf life specification (80% of stated potency). The studies provided to support the excursion demonstrate the same trends for potency and therefore only support an excursion of ≤ 18 hours at ≤ 25°C, followed by 3 months storage at ≤ 25°C after which the product should not be returned to refrigeration. There is no data provided demonstrating that an excursion of 18 hours at +25°C followed by 36 months at 2 to 8°C will not produce the same downward trend in potency.

Therefore, approval of the proposed excursion during shipping cannot be recommended. An application should be made post-approval in the form of a Category 3 application[6]. In line with TGA Guidance document 14.4 *Specific requirements on stability of biological medicines* and Part 4.3 hours of the Minor Variation Guidelines, this application should provide data demonstrating that if the product is subjected to 18 hours at +25°C on release, there are no downward trends evident during the remaining shelf life of 36 months at 2 to 8°C (worst case scenario) that would result in a product released at the lower end of the release specification not meeting end of shelf life specification.

See also Overall conclusion and Benefit/Risk Assessment below for further discussion of Quality issues.

Proposed conditions of registration for the delegate

Batch release testing and compliance with certified product details (CPD)

1. It is a condition of registration that all batches of Afstyla lonoctocog alfa (rch), powder (and solvent) for injection imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
2. It is a condition of registration that each batch of Afstyla lonoctocog alfa (rch), powder (and solvent) for injection imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.

The sponsor must supply:

a. Certificates of Analysis of all active ingredient (drug substance) and final product.

b. Information on the number of doses to be released in Australia with accompanying expiry dates for the product and diluents (if included).

c. Evidence of the maintenance of registered storage conditions during transport to Australia.

d. 5 containers of each batch for testing by the TGA Laboratories Branch together with any necessary standards, impurities and active pharmaceutical ingredients (with their Certificates of Analysis) required for method development and validation.

This batch release condition will be reviewed and may be modified on the basis of actual batch quality and consistency. This condition remains in place until you are notified in writing of any variation.

[6] Minor variation application

Certified product details

The Certified Product Details (CPD), as described in Guidance 7: *Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM)* in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

IV. Nonclinical findings

Introduction

The overall quality of the nonclinical dossier was satisfactory and consistent with other drugs of the same pharmacological class to which lonoctocog alfa belongs and which have been approved by the TGA for similar indications, including octocog alfa (as approved in 1998, 2001, 2001 and 2005); moroctocog alfa (2009) and turoctocog alfa (2014). All safety related studies were Good Laboratory Practice (GLP) compliant. Despite the duration of the studies being limited due to the development of anti-drug antibodies in both rats and monkeys, this is consistent with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline[7] S6 (R1) and is generally offset by the extensive history of safe rFVIII clinical use.[8] Monkeys administered with mid and high doses of lonoctocog alfa in a repeat-dose toxicity study exhibited transient episodic body tremors remains unexplained and without a clear mechanistic basis and should therefore be considered further in the context of available clinical data.

Pharmacology

Primary pharmacology

FVIII is an endogenous plasma glycoprotein that promotes the conversion of prothrombin to thrombin upon activation of the coagulation cascade, ultimately leading to blood clotting. Lonoctocog alfa is an rFVIII that is intended to promote haemostasis in FVIII deficient patients (Haemophilia A), either as prophylaxis or for treatment of an existing bleeding episode.

In vitro, lonoctocog alfa was shown to promote thrombin formation in both rat and monkey plasma in a concentration dependent manner (1 to 30 IU/mL), consistent with the primary pharmacology of endogenous FVIII.

Several studies were conducted in FVIII null mice to examine the haemostasis promoting activity of lonoctocog alfa administered by the clinical route, that is intravenously (IV). In vivo drug treatment at 20 IU/kg was shown to increase thrombin generation ex vivo (around 100-fold) and correct the thromboelastic properties of FVIII-deficient plasma, comparable to treatment with octocog alfa. Lonoctocog alfa was also shown to decrease the activated partial thromboplastin time (aPTT) and decrease bleeding at ≥ 15 IU/kg (at

[7] ICH S6(R1)Preclinical Safety Evaluation Of Biotechnology-Derived Pharmaceuticals
[8] International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use: Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals (1997); Current Step 4 version, June 2011.

least 2-fold decrease in blood loss over 30 minutes in a tail bleeding model) comparable to drugs in the same class.

These data show that lonoctocog alfa promotes haemostasis in rat and monkey plasma in vitro and in FVIII deficient mice in vivo, supporting the proposed clinical indication.

Secondary pharmacodynamics and safety pharmacology

No secondary pharmacodynamic studies of lonoctocog alfa were provided. Since lonoctocog alfa is highly homologous to endogenous FVIII which has a specific and well-characterised function within the coagulation cascade, off target secondary effects are not anticipated at clinical lonoctocog alfa exposures.

In safety pharmacology studies (all GLP compliant and administration via the clinical route), cardiovascular effects were examined in dogs and monkeys and respiratory effects in dogs alone. In anaesthetised and conscious dogs, adverse effects on both the cardiovascular and respiratory systems (hypotension, suppressed cardiac function, increased respiratory rate and decreased tidal volume) were observed after the final 1250 IU/kg dose in 2 cumulative dosing studies. The effects were probably attributable to the excipient polysorbate 80, which is present in the dose formulation at 0.02%. It has been reported that dogs are highly sensitive to polysorbate 80, which induces both pseudo-allergic reactions and hypotensive effects, associated with histamine release, in dogs.[9] In contrast, cynomolgus monkeys exhibited no adverse cardiovascular symptoms including blood pressure (BP) and electrocardiogram (ECG) when subjected to the same dosing regimen as dogs (25-fold the clinical dose and around 30-fold the clinical maximal plasma concentration (C_{max}) based on the C_{max} extrapolated from the value at 1500 IU/kg) and after repeated dosing. Respiratory effects were not examined other than in dogs and the effects on renal function and the gastrointestinal system were not examined in any species. Pharmacokinetic studies in dogs were not provided. Central nervous system (CNS) effects were investigated in the repeat dose toxicity study in rats after the first dose. No adverse effects on the CNS were observed at 25 fold the clinical dose (1250 IU/kg compared with 50 IU/kg).

The safety pharmacology testing and repeat-dose toxicity studies with lonoctocog and the extensive clinical experience with several drugs of the same class are sufficient to allay any significant concerns for the major organ systems in humans.

Pharmacokinetics

Lonoctocog alfa exhibited a moderate plasma half-life in mice (15 h) and monkeys (around 10 h) and a short half-life in rats (2 to 5 h), compared with the elimination half-life of 10 to 15 hours in patients. The plasma drug concentration (C_{max}, first sampling time at 0.25 h) and area under the curve (AUC) were proportional to dose in monkeys over a dose range from 50 to 1500 IU/kg; in rats, these parameters increased linearly, but were not quite proportional, to dose. The pharmacokinetic profile of lonoctocog alfa was similar to the profiles of Helixate (also known as Kogenate) and Refacto AF in mice and monkeys, but lonoctocog alfa is eliminated slower than Advate (half-life of 15 hours compared with 8 hours in mice, and 10 hours compared with around 5 hours in monkeys).

Repeat-dose pharmacokinetic data from rats and monkeys were unavailable or limited, as the FVIII level in most animals was below the lower limit of quantification (LLOQ) by

[9] Picaut P et al. (1994) Polysorbate 80, Toxicological evaluation after single intravenous administration in rats, mice, dogs and monkeys. Toxicol. Lett. 74:65.

28 days. This was attributed to the formation of anti-drug antibodies which were detectable as early as 6 days of repeat-dosing in high dose (500 IU/kg/day) monkeys.

Specific studies on the distribution, metabolism and excretion of lonoctocog alfa were not performed but are anticipated to parallel those of endogenous FVIII. This is supported by distribution studies for 2 drugs of the same class approved by the TGA, turoctocog alfa and efmoroctocog alfa, as described in the relevant AusPARs. The absence of metabolic studies in this application is supported by ICH guideline S6 (R1).[8]

Pharmacokinetic drug interactions

No drug interaction studies were performed. As a protein substance, lonoctocog alfa is not expected to have pharmacokinetic drug interactions with other medicines.

Toxicology

Acute toxicity

A single dose of lonoctocog alfa was administered IV (the clinical route of administration) to rats and monkeys and the acute toxicity was observed over the ensuing 5 days. The maximum non-lethal dose was 1500 IU/kg in both species, 30-fold the maximum clinical dose. In monkeys, the C_{max} and exposure (AUC) values elicited by this dose were around 35 and 20-fold, respectively, those observed clinically. In contrast, the exposure ratio in rats was modest, with C_{max} and AUC values around 20 and 4-fold those observed clinically. Effects were minor and either not dose-dependent, occurred only in one sex, or were not observed in repeat-dose toxicity studies. Lonoctocog alfa therefore presents a low acute toxicity risk.

Repeat-dose toxicity

Two GLP compliant repeat-dose toxicity studies were conducted in which lonoctocog alfa was administered IV daily for 4 weeks in rats and monkeys. The choice and number of species was appropriate in light of the pharmacodynamics and pharmacokinetics of lonoctocog alfa and drugs of the same class that are already approved by the TGA, and existing knowledge of FVIII biology. The route of administration was equivalent to the clinical route. The dosing regimen was more frequent than the intended clinical frequency of 3 times per week for prophylaxis; however, for the treatment of accidental or surgery-related bleeding, lonoctocog alfa is intended to be administered up to 3 times in 24 hours. The duration of the studies is appropriate and is in accordance with ICH guideline S6 (R1) given the formation of anti-FVIII antibodies (by 15 days in rats and as early as 6 days in monkeys) and resultant acquired haemophilia that develops in both species.[8] Only data obtained prior to the appearance of anti-FVIII are therefore toxicologically informative.

Relative exposure

Exposure parameters after repeat dosing for 4 weeks in rats and monkeys were either unavailable or unreliable due to the formation of neutralising anti-FVIII antibodies. For the calculation of monkey:human exposure ratios, monkey area under the curve from time zero to infinity ($AUC_{0-\infty}$) values normalised to a weekly exposure (see Table 5, below) were derived by multiplying the AUC value after a single dose of lonoctocog alfa (mean for males and females in the repeat dose study, Study APQ0014) by 7. Likewise, the estimated weekly exposure in humans (also shown in Table 5) was obtained by multiplying the $AUC_{0-\infty}$ from a single dose (reported in Study 1001, Part 3) by 3, the number of doses of 50 IU/kg (maximum single recommended dose) as prophylaxis each week. Since single doses in monkeys elicited AUC values that were highly proportional to dose over the range of 50 to 1500 IU/kg (Study APQ0011) and the half-life in monkeys was around 10 hours,

normalised AUC values calculated in the above way are considered to provide a valid estimate of repeat-dose exposure ratios prior to the formation of neutralising anti-drug antibodies (around 6 days in monkeys).

Table 5. Relative exposure in repeat-dose toxicity studies

Species	Study (Study no.)	Dosing frequency/wk	Cumulative dose[1] (IU/kg/week)	$AUC_{0-\infty}$ [2] (IU·h/mL)	Exposure ratio[4]
Monkey (cynomolgus)	4 weeks (Study APQ0014)	7	350	17	2
			1050	42[3]	5
			3500	156[3]	19
Human (Haemophilia A patients)	PK study (Study 1001-Part 3)	3	150	18.8	–

1) The daily (repeat dose) in monkeys and the on demand prophylactic dose in humans (50 IU/kg) multiplied by weekly dosing frequency; 2) data are for the sexes combined at the first sampling occasion (Day 1); 3) AUC_{0-24} values were used ($AUC_{0-\infty}$ values could not be accurately calculated); 4) animal: human ratio of plasma AUC values normalised to weekly exposure by multiplying the individual AUC values by the indicated dosing frequency.

Major toxicities

The principal noteworthy consequence of repeat lonoctocog alfa treatment was a modest to pronounced prolongation of the aPTT in rats and monkeys. Rather than drug toxicity, this is attributed to the formation of antibodies towards lonoctocog alfa, detected in the sera of both species as early as Day 5 after commencement of the repeat-dosing regimens, which likely cross-reacted and thereby reduced the levels of endogenous FVIII. This is consistent with the total plasma FVIII levels at the completion of the 4 week repeat-dose study being below starting levels for at least 2 out of 3 monkeys in each group that received intermediate and high doses and below the limit of quantitation in rats.

Beginning from Day 5 through to the completion of the study, monkeys of both sexes that received intermediate and high doses (150 and 500 IU/kg/day) were observed to exhibit transient episodic tremors at varying times following dose administration. The sponsor noted that the onset of the tremors (Day 5) coincided with detection of anti-drug antibodies in the sera of the animals and suggested the tremors might be due to activation of the immune system. However, there are no data in this study to substantiate this or other reasonable hypotheses as to the mechanistic basis of the tremors, such as adverse findings on brain histopathology. The data do suggest that the tremors are related to the test article (no tremors were observed in control or low dose animals) and are therefore potentially toxicologically significant. The clinical relevance of this finding is unclear, but should it occur in patients, it would be monitorable.

Ovary weight was shown to be increased in a minority of rats dosed with 250 and 1250 IU/kg/day by 4 weeks. Macropathology and histopathology analyses in these rats revealed that the ovary weight changes were paralleled by periovarian sac distension and cystic bursa. Although these changes showed a dose-dependent trend, the grade of cystic bursa was minimal and periovarian sac distension was generally unilateral. In light of the absence of a plausible mechanistic link between FVIII and the ovarian findings, and the absence of notable pathological ovarian findings in nonclinical studies for other drugs of

the same class and the provided studies in monkeys dosed with lonoctocog alfa or other recombinant FVIII, the observed ovarian changes in lonoctocog alfa treated rats are considered of minor toxicological concern.

Transient, mild increases in body temperature in rats treated with lonoctocog alfa are consistent with an acute inflammatory response to a foreign antigen, namely recombinant human FVIII.

Thrombogenicity

A GLP compliant single dose study in rabbits (jugular vein stasis model) was conducted to examine the in vivo thrombogenicity activity of lonoctocog alfa in comparison to Refacto. Thrombus incidence and weight dose-dependently increased but were similarly low for both drugs; only the incidence reached statistical significance with dosing at 1000 IU/kg (20 times the maximum clinical dose) based on rabbit and human body weights of 3 and 50 kg, respectively). Given the similarity in thrombogenic effect between lonoctocog alfa and Refacto and the animal: human dose ratio at which a mild effect was observed, these findings are of minor toxicological concern.

Genotoxicity

Genotoxicity studies were not performed. Lonoctocog alfa is not expected to interact with DNA and genotoxicity studies are not required under ICH guidelines S6 (R1).[8]

Carcinogenicity

Carcinogenicity studies were not performed. Lacking only the B domain plus 4 amino acids of the *a3* domain compared to the endogenous FVIII polypeptide, the primary amino acid sequence of lonoctocog alfa is highly similar to its endogenous counterpart. Upon activation by thrombin-mediated cleavage in vivo, the amino acid sequence of lonoctocog alfa is identical to endogenous FVIII. In vivo carcinogenicity studies in rodents are also not feasible due to the development of antidrug antibodies, as observed in repeat-dose toxicity studies. Given the nature of the drug and the above considerations, the lack of carcinogenicity studies is both acceptable and in accordance with ICH guideline S6 (R1).[8]

Reproductive toxicity

Reproductive toxicity studies were not performed. This is acceptable given the nature of the drug, the long history of rFVIII clinical use without known adverse reproductive or developmental effects and the lack of notable reproductive system pathology in the repeat-dose toxicity studies. Reproductive toxicity studies have generally not been included in nonclinical dossiers for drugs of the same class already approved by the TGA.

Pregnancy classification

No Pregnancy Category has been proposed by the sponsor. Haemophilia A is uncommon in women and thus data on the effects of recombinant FVIII during pregnancy are lacking. Nonclinical data on the reproductive toxicity of lonoctocog alfa are similarly lacking, although the available evidence argues against any adverse effects. Category B2 is therefore considered appropriate, as applied to several rFVIII products approved by the TGA.[10]

[10] TGA Pregnancy Category B2**:** Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.

Local tolerance

Local tolerance was assessed in repeat-dose toxicity studies in rats and monkeys and in a dedicated single-dose study in which rabbits received a single dose of the lonotocog alfa formulation by IV, intra-arterial and peri-venous injection. Macro- and histo-pathological analyses revealed only minor effects that were related to the injection procedure rather than the drug (that is, effects were observed equally in 0.9% saline control and drug-treated animals). There are no concerns for the local tolerance of lonoctocog alfa.

Paediatric use

No studies on juvenile animals were performed, despite lonoctocog alfa being intended for use in both paediatric and adolescent patients. None of the major organs systems are the primary pharmacological target of, or exhibited noteworthy toxicity to, lonoctocog alfa in nonclinical studies. Clinical data also have shown that lonoctocog alfa exhibits comparable pharmacodynamics and pharmacokinetics in juvenile and adult patients. Furthermore, recombinant FVIII has a long history of clinical use in paediatric patients. The lack of nonclinical studies of lonoctocog alfa in juvenile animals is thus considered acceptable and in accordance with relevant European Medicines Agency (EMA) guideline.[11]

Nonclinical summary and conclusions

- The submitted dossier was limited but generally adequate and in accordance with the relevant ICH guideline for the nonclinical assessment of biotechnology derived medicines (ICH S6 (R1)).[8] All safety related studies were GLP compliant.
- In vitro and in vivo, lonoctocog alfa exhibited haemostasis-promoting activity in a variety of assays with similar potency to several drugs of the same class. The proposed clinical indication is supported by nonclinical data.
- Secondary pharmacodynamics were not examined, which is considered acceptable.
- Safety pharmacology studies assessed effects on the central nervous, cardiovascular and respiratory systems. No adverse effects were seen in the CNS studies which were performed in rats. Adverse effects on cardiovascular function (hypotension) and respiration (increased respiratory rate and decreased tidal volume) were observed in dogs in a dose escalation study. The findings were probably due to the excipient polysorbate 80, to which dogs are known to exhibit hypotensive and pseudo-allergic reactions. Similar findings were not observed in cardiovascular studies in monkeys and there was no evidence of impaired cardiovascular or respiratory function in repeat-dose toxicity studies in rats and monkeys. In consideration of the above factors and the history of extensive rFVIII clinical use, no clinically-relevant concerns for effects on major organ systems are raised from the safety pharmacology studies.
- Pharmacokinetic profiles in mice, rats and monkeys were qualitatively similar to that of humans, although lonoctocog alfa is eliminated faster in rats than other species including humans. The elimination half-life of lonoctocog alfa was 10 to 15 hours in mice, and monkeys, similar to the $t_{1/2}$ in patients, while the $t_{1/2}$ was around 5 hours in rats. Exposure was proportional to dose in monkeys and to a lesser degree in rats. Distribution, metabolism and elimination were not examined but are anticipated to parallel those of endogenous FVIII.

[11] European Medicines Agency (2005). EMEA/CHMP/SWP/169215/2005: Guideline on the need for non-clinical testing in juvenile animals of pharmaceuticals for paediatric indications.

- As a recombinant form of human FVIII, lonoctocog alfa is not expected to pharmacokinetically interact with other medicinal products and accordingly no studies were performed.
- Studies in rats and monkeys indicate that lonoctocog alfa administered IV presents a lower acute toxicity risk.
- In repeat-dose toxicity studies up to 4 weeks in rats and monkeys, daily IV dosing elicited drug specific antibodies which were detected in plasma. Consequently, total plasma FVIII levels were significantly reduced and aPTT was concomitantly increased in both species. The duration of studies is therefore considered to be appropriate and in accordance with ICH guideline S6 (R1), and findings in repeat-dose studies beyond the above time-points are therefore of limited toxicological value.[8]
- In monkeys, the only species of the 2 in which the maximum exposure (AUC) was adequate, the principal observation of toxicological concern from repeat-dose studies was transient episodic tremors at 150 or 500 IU/kg/day. The onset of the tremors at around 5 days coincided with the detection of anti-drug antibodies in the plasma of monkeys. The sponsors attribute the tremors to an immune reaction to the drug, although the mechanistic link is tenuous. The tremors may be of genuine toxicological concern, despite no corresponding gross pathology or histopathology findings. However, the immunogenicity of lonoctocog alfa in monkeys and rats is a major confounding factor for the interpretation of nonclinical data concerning its repeat-dose toxicity. The clinical relevance of this finding is unclear, but should it occur in patients, it would be monitorable.
- Minor thrombogenic effects in a rabbit jugular vein stasis model at a high dose relative to the maximum human dose were comparable to those elicited by the FVIII reference drug, Refacto, and are considered to be of minor toxicological concern.
- No genotoxicity, carcinogenicity or reproductive studies were conducted and this is considered acceptable.

There are no nonclinical objections to the registration of lonoctocog alfa based on the nonclinical data provided and evaluated in this report.

V. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

[12]

The 2013 to 2014 Annual Report of the Australian Bleeding Disorders Registry estimated that there were 2,181 subjects in Australia with haemophilia A.[13]

Treatment of haemophilia A is based on the use of replacement factor VIII products. Replacement therapy may be 'on demand' where treatment is given when a haemorrhage

[12] Peyvandi F, et al. The past and future of haemophilia: diagnosis, treatments, and its complications. Lancet. 2016; Published online: February 17, 2016.
[13] National Blood Authority Australia. Australian Bleeding Disorders Registry. Annual Report 2013-2014.

occurs, or prophylactic factor VIII is administered at regular intervals in an attempt to prevent the onset of haemorrhage.

After activation of lonoctocog alfa, it has an amino acid sequence identical to that of activated FVIII formed from endogenous, full-length FVIII.

More details about Afstyla and haemophilia are provided under *Product background* and *Quality fin*dings above.

Guidance

The following EMA guidelines, which have been adopted by the TGA, are considered relevant to the current application:

1. Guideline on the Clinical Investigation of the Pharmacokinetics of Therapeutic Proteins.[14]
2. Guideline on clinical investigation of recombinant and human plasma-derived factor VIII products.[15]

The 2011 EMA guideline on FVIII products has recently been updated.[16] However, this revised version did not come into effect in the EU until May 2016, after the sponsor had completed the pivotal studies contained in this submission. At the time of writing, the 2016 revision had not been adopted by the TGA.

Contents of the clinical dossier

The submission contained the following clinical information:

- 1 pivotal Phase I/III clinical trial conducted in adults and adolescents (Study 1001) that provided data on pharmacokinetics, efficacy and safety;
- 1 pivotal Phase III clinical trial conducted in children aged < 12 years (Study 3002) that provided data on pharmacokinetics, efficacy and safety;
- An interim study report on an ongoing open label extension trial (Study 3001) that provided safety data only.
- 1 population pharmacokinetic (PK) analysis.
- A Clinical Overview, Summary of Biopharmaceutics, Summary of Clinical Pharmacology, Summary of Clinical Efficacy and Summary of Clinical Safety.

Paediatric data

The submission included paediatric pharmacokinetic, efficacy and safety data.

Good clinical practice

All clinical study reports included an assurance that the studies had been conducted in accordance with the ICH Good Clinical Practice guidelines and the Declaration of Helsinki.

14 European Medicines Agency. (2007). Guideline On The Clinical Investigation Of The Pharmacokinetics Of Therapeutic Proteins (CHMP/EWP/89249/2004).
15 European Medicines Agency. (2011). Guideline on clinical investigation of recombinant and human plasma-derived factor VIII products (EMA/CHMP/BPWP/144533/2009)
16 European Medicines Agency. (2016). Guideline on clinical investigation of recombinant and human plasma-derived factor VIII products (EMA/CHMP/BPWP/144533/2009 rev 1).

Pharmacokinetics

Studies providing pharmacokinetic data

The 2 pivotal studies in this submission (Studies 1001 and 3002) provided PK data.

Evaluator's conclusions on pharmacokinetics

The PK of rVIII-SingleChain have been adequately characterised, given the rarity of haemophilia A and the fact that rVIII-SingleChain is a large protein administered IV. The data generated meet the requirements for PK data laid down in the relevant EMA guidelines.

The data demonstrate that administration of rVIII-SingleChain is associated with restoration of FVIII activity in plasma in subjects with severe FVIII deficiency. The FVIII activity levels achieved are modestly increased compared to another recombinant FVIII product registered in Australia (Advate). Compared to adults, children have increased clearance of rVIII-SingleChain and a higher volume of distribution, and as a result achieve lower plasma FVIII activity levels.

Pharmacodynamics

FVIII activity was measured in the 2 pivotal studies submitted. In haemophilia A studies, this is considered to be a PK endpoint and results have therefore been described in the previous section and under *Pharmacokinetics* in Attachment 2. There were no other pharmacodynamic data submitted.

Dosage selection for the pivotal studies

In the 2 pivotal efficacy studies, the dose chosen for each patient was based on the 2012 World Federation on Hemophilia (WFH) Guidelines; the previous FVIII dose used for the patient and any available PK data.

Efficacy

Studies providing efficacy data

The 2 pivotal efficacy studies (Study 1001 and Study 3002) provided efficacy data.

Evaluator's conclusions on efficacy

The pivotal studies complied with the requirements of the EMA guideline for FVIII products.[15] The guideline states that pharmacokinetic endpoints such as incremental recovery, half-life, AUC and clearance are important surrogate endpoints for efficacy for a FVIII product. The PK data for rVIII-SingleChain indicate that the product restores FVIII activity to plasma of subjects with severe FVIII deficiency, with a half-life that is comparable to other FVIII products.

As recommended by the EMA guideline, the 2 pivotal studies were conducted in previously treated patients.

Study 1001: This study examined efficacy in adults and adolescents. This study demonstrated that the efficacy of rVIII-SingleChain in treating bleeding episodes was

assessed as 'excellent' or 'good' in 92.3% of instances. In 92.5% of bleeding episodes, haemostasis was achieved with 1 or 2 injections.

When used as prophylactic therapy, rFVIII-Single Chain was associated with a low rate of spontaneous bleeds (1.6 per year), which was significantly lower than the rate observed in subjects receiving on demand therapy (19.5 per year). A similar reduction was observed for the rate of total bleeds per year.

Study 3002: This study examined efficacy in paediatric subjects aged < 12 years. In this study the efficacy of rVIII-SingleChain in treating bleeding episodes was assessed as 'excellent' or 'good' in 96.3% of instances. In 95.7% of episodes, haemostasis was achieved with 1 or 2 injections.

Prophylaxis with rVIII-SingleChain was associated with a low rate of spontaneous bleeding (1.9 per year), which was lower than the rate observed in subjects receiving on demand therapy (28.7 per year). A similar reduction was observed for the rate of total bleeds per year.

These data indicate that rVIII-SingleChain is effective for prophylaxis therapy and the treatment of bleeding episodes in previously treated patients.

Efficacy in surgery: was assessed in a total of 16 surgeries in 13 subjects. The investigators assessed haemostasis as 'excellent' or 'good' in all cases.

The dosage regimens proposed by the sponsor are appropriate. The recommended dose for prophylaxis in the draft PI is 20 to 50 IU/kg given 2 or 3 times a week. Twice per week and 3 times per week regimens were the most common prophylaxis regimens used in the pivotal studies. Prophylaxis regimens have traditionally aimed to maintain a factor VIII activity level of > 1% at trough. Bleeding episodes are observed infrequently in subjects who are able to maintain such levels.[17] The population PK analysis suggested that the lowest proposed dose (20 IU/kg twice a week) would result in FVIII activity levels of > 1% at trough in 54% of subjects. Therefore, some patients will require higher doses. Each patient will require titration to an appropriate prophylactic dose, as is the case with other FVIII products.

The PK data indicate that rVIII-SingleChain restores FVIII activity levels to a similar degree as other FVIII products. The dosing regimens proposed by the sponsor for the treatment of haemorrhage, for prophylaxis and for use in surgery are similar to those approved for other FVIII products (with the exception of Eloctate, which is a long acting FVIII product).

No specific dose amendments are proposed for paediatric use, although children had an increased clearance compared with adults. However, the PI contains a statement that higher doses or more frequent dosing may be required in children. This approach is similar to that taken for other FVIII products registered in Australia.

Efficacy has not been studied in previously untreated patients (PUPs) or in subjects with inhibitors. Studies in these populations are not required prior to registration according to the EMA guideline adopted by the TGA.[15]

Overall the efficacy data are considered adequate to support registration of the product.

[17] Jiménez-Yuste V, et al. Achieving and maintaining an optimal trough level for prophylaxis in haemophilia: the past, the present and the future. Blood Transfus; 2014; 12: 314-9.

Safety

Studies providing safety data

Safety data were collected in the 2 pivotal studies. In addition, the sponsor provided safety data from Study 3001, an open long term extension study for subjects who had completed one of the pivotal studies. This study enrolled a total of 154 subjects (132 subjects from Study 1001 and 22 subjects from Study 3002).

Patient exposure

A total of 258 subjects were treated with rVIII-SingleChain in the submitted studies. The median number of exposure days was 63.5 in Study 1001 and 58.5 in Study 3002. For those subjects who continued into Study 3001, the median total exposure was 135.5 days.

Mean study duration was 8.5 months for Study 1001, 6.0 months for Study 3002 and 5.3 months for Study 3001.

The extent of patient exposure meets the requirements of the EMA guideline for a new FVIII product.[15]

Safety issues with the potential for major regulatory impact

Inhibitor development

No subjects developed FVIII inhibitors in any of the 3 studies.

One subject in Study 3002 was noted to have a low titre inhibitor (0.90 Bethesda Units (BU)/mL) at the 1 month visit. However, re-testing of the sample collected at screening demonstrated a pre-existing low titre inhibitor (3.46 BU/mL). Due to a laboratory process error, the screening sample had initially been reported as negative.

Characterisation of the rate of inhibitor formation was one of the primary objectives of Study 1001.

For calculating the incidence rate, the numerator included all subjects with inhibitors regardless of exposure days (ED) to rVIII-SingleChain, and the denominator included subjects with at least 50 EDs plus subjects with less than 50 EDs but with an inhibitor. A 2 sided 95% CI was calculated. An acceptable rate of inhibitor formation would be concluded if the upper confidence limit was less than 6.8%.

There were no subjects with inhibitors and 120 subjects with at least 50 EDs. The calculated rate of inhibitor formation was 0% (95% CI: 0 to 3.0%). As the upper 95% CI was < 6.8%, the rate of inhibitor formation was considered acceptable.

Antibodies against rVIII-SingleChain (non-neutralising anti-drug antibodies)

In all 3 studies there were a proportion of subjects who were positive for such antibodies at Baseline.

The incidence of subjects who were negative at Baseline and became positive after Baseline was 2.3% in Study 1001, 11.9% in Study 3002 and 0% in Study 3001.

The development of anti-drug antibodies (ADA) was not associated with any apparent increased risk of adverse events (AE) or loss of efficacy. There were 14 subjects who developed ADAs and had PK data. According to the sponsor the PK profiles in these subjects were similar to those in subjects without ADAs.

Post-marketing data

There were no post-marketing data contained in this submission.

Evaluator's conclusions on safety

The total number of subjects exposed to rVIII-SingleChain in the submitted clinical studies was 258. Of these, a total of 185 subjects received at least 50 exposure days of treatment. This is in excess of the total number of subjects required by the relevant EMA guideline adopted by the TGA (a total of 100 subjects with at least 50 exposure days).[15]

The major safety issue with FVIII products is the development of inhibitors. No cases of inhibitor development were observed in the submitted studies of rVIII-SingleChain. However, only previously treated patients at low risk of inhibitor development were enrolled in the submitted studies. In previously untreated patients (PUPs) with severe haemophilia A, inhibitors form in approximately 30% of subjects, usually during the first 30 exposure days.[18] A recently published randomised trial demonstrated that the incidence of inhibitor development in PUPs is higher with recombinant products than with plasma derived products.[19] The EMA guideline requires that a study of safety, efficacy and PK in PUPs should be commenced prior to a marketing authorisation of a novel FVIII product, and the sponsor is enrolling PUPs in an additional arm of Study 3001 (Arm 2). The sponsor should be asked to provide a summary of any available data on inhibitor development in these subjects.

The adverse event profile of rVIII-SingleChain observed in the submitted studies was generally consistent with that expected for a FVIII product. Cases of hypersensitivity were observed. However, only one subject discontinued treatment due to a hypersensitivity event. Other cases were able to continue treatment with antihistamine premedication. No cases of anaphylaxis were observed. There were no thromboembolic events reported.

Other AEs observed commonly in the submitted studies were non-specific that might commonly be observed in the general population (nasopharyngitis, arthralgia, headache, rash, cough, pyrexia). The proportion of such events assessed as being related to the drug was low.

Overall the safety profile of rVIII-SingleChain is considered acceptable.

First round benefit-risk assessment

First round assessment of benefits

The benefits of rVIII-SingleChain in subjects with haemophilia A are:

- Restoration of plasma FVIII activity;
- A reduction in the incidence of bleeding episodes when a prophylaxis regimen is used;
- Adequate control of bleeding episodes when they occur, usually with 1 or 2 injections only;
- Adequate control of bleeding during surgical procedures.

[18] Peyvandi F et al. The past and future of haemophilia: diagnosis, treatments, and its complications. Lancet. 2016; Published online: February 17, 2016.
[19] Peyvandi F et al. A Randomized Trial of Factor VIII and Neutralizing Antibodies in Hemophilia A. N Engl J Med. 2016; 374: 2054-64.

First round assessment of risks

The risks of rVIII-SingleChain in subjects with haemophilia B are:

- Hypersensitivity reactions;
- Other minor adverse events (for example, arthralgia, headache, rash, cough, and pyrexia).
- Although no cases of inhibitor development occurred in the submitted studies, it can be expected that such cases will occur.

First round assessment of benefit-risk balance

The benefit-risk balance of rVIII-SingleChain in the treatment of haemophilia A is favourable.

First round recommendation regarding authorisation

It is recommended that the application for registration be approved.

Clinical questions

The clinical evaluator had the following clinical questions for the sponsor:

1. The proposed correction factor for converting one stage assay results to chromogenic assay results is 1.8. It is noted that in the approved prescribing information for the United States, the correction factor is 2.0. Please comment on the reasons for this difference.
2. In Study 3002, the primary endpoint was the investigator's overall assessment of haemostatic efficacy, which consisted of a 4 point scale (excellent, good, moderate, poor/none). The study report, protocol and statistical analysis plan did not contain definitions of the terms 'excellent', 'good' and so on. Please clarify whether any definitions were provided to investigators, and if so, please provide a copy.
3. Please provide a summary of any available data on inhibitor development and hypersensitivity events in previously untreated patients (PUPs) treated with rVIII-SingleChain in Study 3001 (Arm 2).

Second round evaluation and second round benefit-risk assessment

A second round clinical evaluation report was not completed for this submission, as only 3 targeted clarification questions were posed to the sponsor.

VI. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP): EU-RMP, version 1.0 dated 25 November 2015 with a data lock point (DLP) of 28 August 2015 and an Australian Specific Annexe (ASA) version 1.0 dated 25 January 2016 which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown below in Table 6.

Table 6. Sponsor's Summary of ongoing safety concerns

Summary of safety concerns	
Important identified risks	Hypersensitivity and anaphylactic reactions
Important potential risks	Development of inhibitors
	Dosing errors based on assay type (ChS versus OS) used for monitoring of FVIII levels
	Development of antibodies against CHO host cell proteins
Missing information	Experience of inhibitor formation in PUPs
	Experience in pregnancy and lactation, including labour and delivery
	Experience in geriatric patients (65 years and above)
	Experience of use in patients for ITI (off label use)

Note: ChS = chromogenic substrate; OS = one stage assay; CHO = Chinese hamster ovary; PUPs = previously untreated patients; ITI = immune tolerance induction.

Pharmacovigilance plan

The sponsor has proposed routine pharmacovigilance[20] for all safety concerns. This includes the use of follow-up questionnaires for pregnancy, allergic and anaphylactic reactions and development of inhibitors or lack of efficacy. An additional pharmacovigilance activity, in the form of a clinical trial, has been proposed for the following safety concerns as shown below in Table 7.

Table 7. Additional pharmacovigilance activities

Safety Concern	Additional activity	Proposed actions/ outcomes	Planned submission date
Hypersensitivity and anaphylactic reactions	Clinical Trial 3001	To provide further safety	Projected submission

[20]Routine pharmacovigilance practices involve the following activities:
- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labeling;
- Submission of PSURs;

Meeting other local regulatory agency requirements.

Safety Concern	Additional activity	Proposed actions/ outcomes	Planned submission date
Development of inhibitors	(including enrolment of PUPs)	and efficacy data in patients	date for final CSR is Q4 2021
Development of antibodies against CHO host cell proteins			
Experience of inhibitor formation in PUPs			
Usage and safety in geriatric patients			
Hypersensitivity/anaphylactic reactions and development of inhibitors to FVIII	Participation in European Haemophilia Safety Surveillance system (EUHASS) to collect longterm Safety data.[1]	To review the available post-marketing data for safety concerns	Interim updates based on EUHASS reports will be included in each PSUR

1) Additional pharmacovigilance activity added in EU-RMP version 2 (post first round).

Risk minimisation activities

Only routine risk minimisation activities[21] are planned for the identified safety concerns. The activities proposed for Australia are consistent with those proposed for the EU.

Reconciliation of issues outlined in the RMP report

Table 8 summarises the RMP evaluator's first round evaluation of the RMP, the sponsor's responses to issues raised and the RMP evaluator's evaluation of the sponsor's responses.

Table 8. Reconciliation of first round recommendations to the RMP

Reconciliation of first round recommendations to the RMP
***Recommendation 1*:** Any safety concerns identified by the clinical or nonclinical evaluators that impact on the safety specifications should be addressed in a revised RMP.
Sponsor's response: The sponsor confirms that the nonclinical evaluator did not identify any safety concerns. With regards to the clinical evaluation, the evaluator made a request relating to safety in Clinical Question 3. As discussed in response to Clinical

[21] Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

Reconciliation of first round recommendations to the RMP
Question 3, one PUP enrolled in Arm 2 of Study 3001 developed a low titre inhibitor. The risk of developing inhibitors with Afstyla is already indicated as a safety concern in EU RMP.
RMP Evaluator comment: No safety concerns were identified by the evaluators, therefore the sponsor's response is adequate.
Recommendation 2: The 3 follow up questionnaires (for pregnancy, allergic and anaphylactic reactions, and development of inhibitors or lack of efficacy) should be appended to the ASA, and the sponsor should ensure that they are relevant for use in the Australian context.
Sponsor's response: The sponsor confirms that the 3 follow-up questionnaires are relevant for use in the Australian context and have been appended to the ASA). It should be noted that the EU-RMP was updated during EMA evaluation (to version 2.0) and this is provided. Accordingly, the ASA has also been updated to align with the most current version of the EU-RMP.
RMP evaluator comment: The follow up questionnaires are appended to the updated ASA version 2.0 dated 23 September 2016 and are relevant for use in Australia. The ethnicity section is more appropriate for a North American population but there are categories that can be applied to the Australia population: Asian, Caucasian/White, Other Pacific Islander and Other.
Recommendation 3: The Consumer Medicine Information (CMI) should be revised to address the concerns regarding the suitability of the instructions for use and appropriateness of the language used, as has been described.
Sponsor's response: An updated CMI is provided in line with the evaluator's recommendations.
RMP evaluator comment: The sponsor has updated the CMI. The language is more consumer friendly, diagrams have been inserted, there is advice on how to identify different strengths as well as advice re-seeking help from healthcare professionals to ensure correct administration. The sponsor has not provided a space to record batch details and has stated in its response that this is consistent with CMIs for similar products, and that the CMI is not considered the most practical means to record treatment details. This argument is reasonable.

Summary of recommendations

There are no outstanding issues.

Wording for conditions of registration

Any changes to which the sponsor has agreed should be included in a revised RMP and ASA. However, irrespective of whether or not they are included in the currently available version of the RMP document, the agreed changes become part of the risk management system.

The suggested wording is:

Implement EU-RMP (version 2.0, 8 July 2016, data lock point 28 August 2015) with Australian Specific Annex (version 2.0, 23 September 2016) and any future updates as a condition of registration.

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations.

Quality

At the time of writing this overview, 2 outstanding issues were identified by the lead quality evaluator.

The first issue relates to specifications for the excipients histidine and polysorbate 80:

- The lead quality evaluator identified that the excipients histidine and polysorbate 80 exceed the compendial requirements.
- In the sponsor's response, the sponsor acknowledged the specifications for the excipients histidine and polysorbate 80 exceed the compendial requirements and the sponsor agreed to tighten these specifications, as requested, in accordance with the Ph. Eur 01/2008:1643 Human coagulation factor VIII (rDNA) requirements. The adjusted specification ranges have been updated in the relevant CTD sections.

However, after evaluation of these updated specification ranges, the evaluator states that the new specifications submitted still do not meet the Ph. Eur requirement to be 80% to 120% of the stated content.[22] The second issue relates to a proposed temperature excursion during transport of up to +25°C for ≤ 18 hours. This was requested by the sponsor in their second round response. The sponsor provided a justification for this request with accompanying data. This was reviewed by the lead quality evaluator who stated the following:

'It is stated that a stability study provided in the original submission (Study 808-016 - 3 months and 3 weeks at +25°C followed by 36 months at 2-8°C) supports this, as well as a new study (40°C for 1 week, followed by 3 months at +25 °C and 33 months at 2-8°C). However, Study 808-016 cannot be located in the original submission as stated […] furthermore, neither study supports the proposed temperature excursion of ≤ 18 hours at ≤ 25°C for the following reason:

> *'Stability data previously evaluated shows that when subjected to + 25°C for three months and returned to 2 to 8°C there is a significant downward trend in potency so that if product was released at the lower end of release specification (90% of stated potency), the product will not meet end of shelf life specification (80% of stated potency). The studies provided to support the excursion demonstrate the same trends for potency and therefore only support an excursion of ≤ 18 hours at ≤ 25°C, followed by three months storage at ≤ 25°C after which the product should not be returned to refrigeration. There is no data provided demonstrating that an excursion of 18 hours at +25°C followed by 36 months at 2 to 8°C will not produce the same downward trend in potency.*

[22] Following the Delegate's overview the sponsor submitted a Pre-ACM Response as follows: '*As requested, the specifications for the excipients histidine and polysorbate 80 have been amended in accordance with the Ph. Eur 01/2008:1643 Human coagulation factor VIII (rDNA) requirements and the relevant CTD sections have been updated ……. Module 2.3.P was revised accordingly. Specifications for histidine and polysorbate 80 have been set as follows: [information redacted].*'

Therefore approval of the proposed excursion during shipping cannot be recommended. An application should be made post-approval in the form of a Category 3 application. In line with TGA Guidance document 14.4 Specific requirements on stability of biological medicines and Part 4.3 hours of the Minor Variation Guidelines, this application should provide data demonstrating that if the product is subjected to 18 hours at +25°C on release, there are no downward trends evident during the remaining shelf life of 36 months at 2 to 8°C (worst case scenario) that would result in a product released at the lower end of the release specification not meeting end of shelf life specification.''

It is important to note that a third issue of the shelf life conditions for the drug product was resolved following the sponsors responses to the evaluation reports.

In summary, after additional evaluation of the sponsor's response to the issues of:

- specifications for the excipients histidine and polysorbate 80; and
- approval of the proposed excursion during shipping; the lead quality evaluator advises that these issues have not been satisfactorily resolved.

The evaluation of container safety, infectious disease/viral safety, microbiology (sterility), and endotoxin safety evaluation were satisfactorily completed with no outstanding issues at the time of this overview.

Conditions of registration have also been proposed.

Nonclinical

There are no nonclinical objections to the registration of lonoctocog alfa based on the nonclinical data provided and evaluated in the nonclinical evaluation report.

Pregnancy category B2 was recommended by the nonclinical evaluator: '*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*'.[10]

The sponsor has accepted this recommendation.

The sponsor has also accepted the TGA's recommendations regarding use in lactation.

The nonclinical evaluation report notes that during the repeat-dose studies in monkeys, '*almost all' subjects were noted to develop episodic body tremors at 150 or 500 IU/kg/day. This finding was attributed to an immune reaction to the drug with the tremors stated to coincide with the detection of ADA in the sera. The nonclinical evaluator stated that the data do suggest that the tremors are related to the test article (no tremors were observed in control or low dose animals) and are therefore potentially toxicologically significant. The evaluator states that tremors may be of genuine toxicological concern, despite no corresponding gross pathology or histopathology findings. However, the immunogenicity of lonoctocog alfa in monkeys and rats is a major confounding factor for the interpretation of nonclinical data concerning its repeat-dose toxicity. The nonclinical evaluator concludes that 'monkeys administered mid and high doses of lonoctocog alfa in a repeat-dose toxicity study exhibited transient episodic body tremors remains unexplained and without a clear mechanistic basis and should therefore be considered further in the context of available clinical data'*. Further comments on this are provided in the discussion section below.

Clinical

The clinical data included 2 pivotal clinical studies that addressed the role of rVIII-SingleChain for on demand and prophylaxis treatment of adults and children with severe haemophilia A (named Study 1001 and Study 3002). Two additional studies were provided: an interim study report named Study 3001 providing safety data only; and a population PK analysis.

A range of PK, efficacy and safety endpoint measurements were identified in each study. A comprehensive description of each study is provided in Attachment 2. For the purpose of this overview, a brief summary of each study will be provided here, with subsequent sections of this report regarding pharmacology, efficacy and safety used to provide specific study design detail and results.

Study 1001

Study 1001 was a Phase I and III, open label clinical trial conducted in adults and adolescents with severe haemophilia A. There was no randomisation or blinding used in the study. This study provided data on PK, efficacy and safety (see comprehensive description in Attachment 2). A total of 175 subjects were enrolled in the study and 174 received treatment. The study consisted of 3 parts:

- *Part 1:* included a total of 27 subjects aged over 18 years with severe haemophilia A (mean age 35.4 years, range 19 to 60yrs). All subjects received a single IV dose of 50 IU/kg of Advate (recombinant FVIII/octocog alfa) followed by a single IV dose of 50 IU/kg of rVIII-SingleChain (after a wash out period of 4 days) to enable a comparison of the PK of the 2 products.
- *Part 2:* The 27 subjects enrolled in Part 1 were continued on open-label treatment with rVIII-SingleChain. The first 5 subjects were to receive on demand treatment. The remaining subjects could be treated with either on demand or prophylaxis treatment. For prophylaxis, rVIII-SingleChain was administered at a dose of 20 to 40 IU/kg every second day, or 20 to 50 IU/kg 2 to 3 times per week, or at other doses and frequencies at the investigator's discretion. For use during surgery, the dose was individualised based on the type of surgery, any previously obtained PK data for the patient and FVIII levels recommended by WFH guidelines.[2] This part of the study assessed efficacy and safety in these subjects.
- *Part 3:* A total of 147 additional subjects with severe haemophilia A (aged ≥ 12 to 65 years) were enrolled and received open-label treatment with rVIII-SingleChain, either as on demand treatment or prophylaxis for at least 50 exposure days (EDs), with assessment of efficacy and safety. In was planned to enrol approximately 100 subjects in this Part. A subgroup of subjects in Part 3 also underwent PK assessment at baseline (following a single dose of 50 IU/kg of rVIII-SingleChain) and again after 3 to 6 months of treatment.

Major protocol deviations that impacted on the intention to treat (ITT) and per protocol (PP) populations studied are summarised below:

- A total of 17 subjects in the efficacy population were excluded from the per protocol population. All were excluded due to lack of compliance (see definitions of compliance in prophylaxis and on demand use in Attachment 2).

Study 3002

Study 3002 was a Phase III clinical trial conducted in children aged < 12 years. This study provided data on PK, efficacy and safety. There was no randomisation or blinding used in the study. A total of 84 subjects were enrolled and treated. This consisted of a total of

35 subjects in the 0 years to < 6 years group (mean age 3.5 years, minimum age 1 year, maximum age 5 years) and 49 subjects aged > 6 years to < 12 years (mean age 9 years, minimum 6 years, maximum 11 years). The distribution of age in each study group, particularly the < 6 years group is not clear from the data presented in the clinical study report for Study 3002 (see *Clinical questions*). The primary objective was to evaluate the efficacy of rVIII-SingleChain in the treatment of bleeding episodes based on an investigator's 4 point assessment scale. Multiple secondary objectives were also investigated which are identified in the sections on PK, efficacy and safety below.

Study 3002 was made up of a PK period and a treatment period:

- In the PK period, a subgroup of subjects received a single dose of 50 IU/kg of rVIII-SingleChain at Baseline (Day 12).
- All subjects were then enrolled in a treatment period during which rVIII-SingleChain was administered either as on demand or prophylactic therapy for at least 50 EDs.
  - Study treatments:
    - The dose used for the treatment of a bleeding episode was determined by the investigator, based on previous FVIII dose, any available PK data and the subject's bleeding phenotype. The target FVIII activity level was based on WFH guidelines.[2]
    - For prophylactic therapy, subjects received rVIII-SingleChain at a dose of 15 to 50 IU/kg every second day, or 2 to 3 times per week, or at a dose and frequency determined by the investigator based on previous FVIII dosing and available PK data.
  - Treatment was continued until 50 EDs had been reached. This was expected to take approximately 6 months for subjects on prophylactic therapy and up to 2 years for subjects receiving on demand therapy.
  - Treatment with rVIII-SingleChain during major surgery was not permitted and subjects were to be withdrawn from the study if major surgery could not be avoided.

Major protocol deviations that impacted on the ITT and per protocol (PP) populations studied are summarised below:

- Exclusion of 1 subject from the efficacy population. This subject was identified as having a pre-existing inhibitor to FVIII, based on re-examination of the screening blood sample that had initially been reported as negative due to laboratory process error. Although excluded from the efficacy population the subject continued in the study.
- 8 subjects in the efficacy population were excluded from the PP population due to noncompliance with the prescribed dose and/or regimen.

Study 3001

An ongoing, open label, long term extension study for subjects who have completed one of the pivotal studies (Study 3001 and Study 3002). At the time of the current data submission to the TGA, this study had enrolled a total of 154 subjects (132 subjects from Study 1001 and 22 subjects from Study 3002).

Formulation

The proposed product is a lyophilised powder, to be reconstituted with WFI for IV injection. 7 strengths are proposed in the current submission: 250, 500, 1000, 1500, 2000, 2500 and 3000 IU.

The initial submission to the TGA included an additional dose form of 375 IU. On 10 November 2016, the sponsor informed the TGA that they do not wish to pursue registration of the 375 IU presentation of Afstyla. This presentation is not registered in the US and has been removed from the Afstyla application in the EU.

As noted above, the dose forms of 1500 IU and 2500 IU are not approved for use in the US but have been approved for use in the EU. The reason for the exclusion of the 1500 IU and 2500 IU dose forms in the US has not been addressed by the sponsor.

According to the overall summary of quality in the submission the composition of the drug product used in all clinical studies and the drug product proposed for commercial supply is the same. Study 1001 compared the PK of FVIII activity following use of 3000 IU or 250 IU vials. Although not a formal bioequivalence study, the results suggested that the 2 vial strengths produced comparable PK.

Pharmacokinetics (PK)

A total of 3 studies provided PK data. These are Study 1001, Study 3002 and a population PK analysis.

The PK of rVIII-SingleChain was measured using FVIII activity, in compliance with EMA guidelines.[14] Two assays are commonly used to measure FVIII activity in plasma. These are the chromogenic substrate (ChS) assay and the one stage (OS) assay. During the development of rVIII-SingleChain, the sponsor recognised that the OS assay gave results that were lower than the results produced by the ChS assay. Preclinical data indicated that the ChS assay more accurately predicted effectiveness and hence the ChS assay was chosen to assign potency for the product. In the clinical PK studies both the ChS and OS were used to assess FVIII activity in plasma. The OS assay gave results that were approximately 45% lower than the results produced by the ChS assay. The sponsor recommends the use of the ChS assay, if available, for assessing FVIII activity in plasma. However, the OS assay is commonly used in clinical practice for assessing FVIII activity in haemophilia A subjects. Therefore, the sponsor is proposing that results obtained with the OS assay can be corrected to align to chromogenic assay results. Initially a conversion factor of 1.8 was proposed, however the sponsor subsequently proposed that a conversion factor of 2.0 be applied. The conversion factor of 2.0 is in line with the US PI document.

The PK aspects of Study 1001 are summarised in Attachment 2. A primary PK objective of the study was to characterise the PK profile of rVIII-SingleChain, with a secondary objective to perform a PK comparison between rVIII-SingleChain and Advate (recombinant FVIII/octocog alfa). PK sampling, analysis and results are summarised in Attachment 2. Blood samples for PK measurements were collected in study Part 1 and Part 3. Samples were analysed for FVIII activity, using both a validated ChS assay and a validated OS clotting assay. The submission included a separate PK report (dated 23 November 2015) which presented a large number of analyses. Analyses were presented for both ChS and OS, FVIII activity levels corrected and uncorrected for the subject's baseline FVIII activity levels, and for various populations (all subjects, only subjects who received a dose within the range of 50 IU/kg ± 10%, only subjects with a baseline FVIII level of < 1%). The clinical evaluator noted that the Advate product used in Part 1 had a labelled potency of 218 IU/mL (according to the OS assay). However according to the ChS assay it had a measured potency of 255.9 IU/mL. The dose of Advate administered was therefore 'higher' than that labelled. 'Dose adjusted' analyses (which took account of this discrepancy) were presented, together with 'dose-unadjusted'

analyses. Non-compartmental analysis methods were used. Notable findings included the following:

- In adults and adolescents, mean incremental recovery after a single dose of 50 IU/kg rVIII-SingleChain was 2.24 IU/dL per IU/kg. This value was similar to that obtained with Advate (2.32 IU/dL per IU/kg).
- C_{max} and incremental recovery were similar for rVIII-SingleChain and Advate. Median time to maximal plasma concentration was at approximately 30 minutes for both products.
  - Mean clearance of rVIII-SingleChain was lower than that of Advate (2.64 versus 3.68 mL/hr/kg)
  - Mean half life of rVIII-SingleChain was slightly longer than that of Advate (14.5 versus 13.3 hours)
  - AUC values for FVIII activity were approximately 37% greater with rVIII-SingleChain than with Advate
  - The proportion of subjects with FVIII activity > 1% at the last sampling point (72 hours) was greater with rVIII-SingleChain (23 of 27 subjects) than with Advate (17 of 27 subjects)
  - FVIII activity levels determined with the OS assay were approximately 45% lower than those determined the ChS assay
  - The PK of rVIII-SingleChain were similar at baseline and after 3 to 6 months of treatment
  - Part 3 of the study compared the PK of FVIII activity following use of 3000 IU or 250 IU vials. Results (based on the ChS assay) are summarised in Attachment 2. PK parameters were comparable with the 2 vial strengths.

A secondary objective of this study was to evaluate the PK profile of rVIII-SingleChain in children (age ≤ 12 years) following a single dose of 50 IU/kg of rVIII-SingleChain on Day 1. PK sampling, analysis and results are summarised in Attachment 2. Samples were analysed for FVIII activity, using both a validated ChS and a validated OS clotting assay. The submission included a separate PK report (dated 13 August 2015) which presented a large number of analyses. Analyses were presented for both ChS and OS, FVIII activity levels corrected and uncorrected for the subject's baseline FVIII activity levels, and for various populations (all subjects, only subjects who received a dose within the range of 50 IU/kg ± 10% (n = 38)). A subgroup analysis was performed comparing 2 age groups: age 0 to < 6 years (n = 20) and age 6 to ≤ 12 years (n = 19).

Notable findings included:

- In children aged < 12 years, incremental recovery for rVIII-SingleChain was lower than in adults (1.60 IU/dL per IU/kg for children aged < 6 years and 1.66 IU/dL per IU/kg for children aged 6 and 12 years; compared to 2.24 IU/dL per IU/kg in adolescents and adults)
- PK profiles were similar for the 2 age subgroups (age 0 to < 6 years (n = 20) and age ≥ 6 to < 12 years (n = 19))
- At the last sampling time (48 hours), 16 of 20 subjects in the younger age group, and 16 of 19 subjects in the older age group had FVIII activity levels > 1%
- FVIII activity levels determined with the OS assay were approximately 45% lower than those determined the ChS assay (similar to that noted in Study 1001)

The results of the population PK analysis are summarised in Attachment 2. The population PK analysis drew on data from the 2 pivotal studies (Studies 1001 and 3002). It was based on a total of 1460 FVIII activity measurements (measured using the ChS assay) collected from 130 subjects. The analysis was conducted using nonlinear mixed effects modelling software (NONMEM Version 7.2). Trough FVIII activity levels were modelled for a range of multiple dosing scenarios. The model predicted that with all dosage regimes simulated, more than 50% of subjects will maintain a trough FVIII level of at least 1%. With the lowest proposed dose regimen of 20 IU/kg twice weekly (on Days 0 and 3) median trough level is predicted to be 1.1 IU/dL on Day 7 and 54.3% of subjects would have a trough level > 1% on Day 7. The population PK analysis did not detect a significant effect of age (in addition to bodyweight) on rVIII-SingleChain PK. The sponsor commented that this was likely to be due to the strong correlation between age and total body weight in children.

Efficacy

The 2 pivotal studies contributed efficacy data (Study 1001 and Study 3002).

The efficacy aspects of Study 1001, including study design and results are presented in Attachment 2. The primary objectives of the study relevant to the efficacy of rVIII-SingleChain included the following:

- Demonstrate efficacy in the prevention and treatment of bleeding events;
- Demonstrate the efficacy of routine prophylaxis treatment over on demand treatment;
- Demonstrate the efficacy of rVIII-SingleChain in surgical prophylaxis.

The study only included previously treated patients with a previous exposure of > 150 EDs to FVIII products. Overall, the inclusion and exclusion criteria were consistent with those recommended in the EMA guideline.[16] Efficacy endpoints were designed to assess efficacy for 3 'indications': treatment of bleeding episodes, prophylactic treatment and use in surgery.

- *Treatment of bleeding episodes:* the primary efficacy endpoint was the rate of treatment success for bleeding episodes defined as a rating of 'excellent' or 'good' on the investigator's overall clinical assessment of haemostatic efficacy 4 point scale. Overall there were a total of 848 bleeding episodes in the study that were treated. The rate of treatment success was 92.3% (95% CI: 88.9 to 94.8%). As the lower limit of the 95% CI was > 70%, efficacy in the treatment of bleeding episodes was determined to be acceptable. Additional sensitivity analyses and subgroup analyses produced similar results to the primary analysis. Other efficacy endpoints were the number of injections of rVIII-SingleChain required to achieve haemostasis, with results showing that in 92.5% of episodes, haemostasis was achieved with 1 or 2 injections (see CER page 14). The rate of treatment success for 'major' bleeding episodes could not be assessed as no 'major' bleeding episodes occurred during the study.
- *Prophylactic treatment:* The primary efficacy endpoint was the annualised spontaneous bleeding rate (AsBR) based on the number of spontaneous bleeding episodes). The AsBR was 19.5 (95% CI: 17.8 to 21.3) spontaneous bleeds per year in the on demand treatment group and 1.6 (95% CI: 1.3 to 1.8) spontaneous bleeds per year in the prophylactic treatment group. The AsBR was reduced by 92% (ratio = 0.08; 95% CI: 0.09 to 0.10). The difference between treatment groups was statistically significant ($p < 0.0001$). Similar results were observed in the Per Protocol population. The results of the other efficacy endpoints for Study 1001 are summarised in Attachment 2. Notable results include:

- An annualised bleeding rate (ABR, based on all bleeding episodes) of 24.9 (95% CI: 23.0 to 27.0) bleeds per year in the on demand treatment group and 2.6 (95% CI: 2.3 to 2.9) bleeds per year in the prophylactic treatment group. The ABR was reduced by 90% (ratio = 0.10; 95% CI: 0.09 to 0.12). The difference between treatment groups was statistically significant ($p < 0.0001$).
- Comparison of AsBR/ABR with historical control (Biostate) showed that prophylaxis with rVIII-SingleChain was associated with a significantly reduced AsBR and ABR when compared to on demand/preventative use of the historical control.
- Consumption of rVIII-SingleChain is summarised in Attachment 2. Most subjects were assigned to a thrice weekly regimen (n = 79, median dose 30.0 IU/kg) or twice weekly regimen (n = 46, median dose 35.0 IU/kg).

· *Use in surgery:* The primary efficacy endpoint was the rate of treatment success defined as an investigator rating of 'excellent' or 'good' on the 4 point efficacy evaluation of surgical treatment scale. A total of 13 subjects underwent a total of 16 procedures (classed as major by the sponsor) in the surgical substudy. This number of major surgeries meets the requirements of the EMA guideline for studying efficacy in the surgical setting.[16] The overall clinical assessment of efficacy was 'excellent' in 15 procedures (93.8%) and 'good' in 1 procedure (6.3%). Overall success rate was therefore 100%. The results of the other efficacy endpoints for Study 1001 are summarised in Attachment 2. Notable results include:

· Total rVIII-SingleChain consumption ranged from 129.11 IU/kg (for removal of internal fixation from an ankle) to 1725.19 IU/kg (for revision of a knee prosthesis).

· Mean observed intraoperative blood loss was 73.3 (± 107.18) mL. This was lower than the mean predicted value (259.3 ± 369.42 mL).

· The mean (± SD) actual volume of packed red blood cells transfused was 0.7 (± 1.78) mL. This was slightly less than the mean predicted volume of 1.1 (± 1.78) mL. There were no other blood products transfused.

· Analysis of the change in haemoglobin levels between baseline, intra-operation and post-operation showed a small reduction in average haemoglobin levels in the post-operative.

The efficacy aspects of Study 3002, including study design and results are presented in Attachment 2. The trial enrolled male subjects with severe haemophilia A, aged < 12 years. Only previously treated patients, with a previous exposure of > 50 EDs to FVIII products, were enrolled. The youngest patient was age 1year however the distribution of age in the group of subjects aged < 6 years is not clear from reviewing the clinical study report data (see *Clinical questions*). Subjects with a history or first order family history of inhibitors were excluded. Overall, the inclusion and exclusion criteria were consistent with those recommended in the EMA guideline.[16] A primary objective of the study was to evaluate the efficacy of rVIII-SingleChain in the treatment of bleeding episodes based on an investigator's 4 point assessment scale. A number of secondary efficacy objectives were also investigated (these are discussed below). Overall there were a total of 347 bleeding episodes in the study that were treated (50 in subjects aged < 6 years and 297 in subjects aged ≥ 6 to < 12 years). The rate of treatment success was 96.3% (95%CI: 91.3 to 98.4%). Sensitivity analysis and multiple subgroup analyses all demonstrated mean success rates of ≥ 90%. Multiple secondary efficacy endpoints were also investigated. Notable results include:

· The AsBR was 28.7 (95% CI: 21.9 to 37.6) spontaneous bleeds per year in the on demand treatment group and 1.9 (95% CI: 1.5 to 2.4) spontaneous bleeds per year in the prophylactic treatment group. For subjects aged <6 years receiving prophylaxis

the AsBR was 0.9 (95%CI: 0.5 to 1.5) and for subjects aged ≥ 6 to < 12 years it was 2.6 (95% CI: 2.0 to 3.3). Among subjects receiving prophylaxis regimens with an initial assigned dose between 15 and 50 IU per dose (n = 74) the AsBR was similar between the different regimens (3.6 for every second day regimens, 1.8 for thrice weekly regimens, 1.9 for twice weekly regimens and 2.5 for other regimens).

- The ABR was 71.5 (95% CI: 60.3 to 84.8) bleeds per year in the on demand treatment group and 5.5 (95% CI: 4.8 to 6.3) bleeds per year in the prophylactic treatment group. For subjects aged < 6 years receiving prophylaxis the ABR was 3.0 (95% CI: 2.3 to 4.0) and for subjects aged ≥ 6 to < 12 years it was 7.4 (95% CI: 6.3 to 8.6).
- The number of injections of rVIII-SingleChain to achieve haemostasis was investigated. In 95.7% of episodes, haemostasis was achieved with 1 or 2 injections. For subjects aged < 6 years the figure was 94.0% and for subjects aged ≥ 6 to < 12 years it was 95.9%.

The clinical evaluator advised that the dosage regimens proposed by the sponsor are appropriate. The recommended dose for prophylaxis in the draft PI is 20 to 50 IU/kg given 2 or 3 times a week. Twice per week and 3 times per week regimens were the most common prophylaxis regimens used in the pivotal studies. Prophylaxis regimens have traditionally aimed to maintain a factor VIII activity level of > 1% at trough. Bleeding episodes are observed infrequently in subjects who are able to maintain such levels.[17] The population PK analysis suggested that the lowest proposed dose (20 IU/kg twice a week) would result in FVIII activity levels of > 1% at trough in 54% of subjects. Therefore, some patients will require higher doses. Each patient will require titration to an appropriate prophylactic dose, as is the case with other FVIII products. Appropriate statements to this effect are present within the proposed PI.

The clinical evaluator concluded that overall, the efficacy data are considered adequate to support registration of the product.

Safety

A total of 3 studies provided safety data. This includes the 2 pivotal studies (Study 1001 and Study 3002). In addition, the sponsor provided safety data from Study 3001; an open long term extension study for subjects who had completed one of the pivotal studies. This study enrolled a total of 154 subjects (132 subjects from Study 1001 and 22 subjects from Study 3002).

A total of 258 subjects were treated with rVIII-SingleChain in the submitted studies. Of these, a total of 185 subjects received at least 50 EDs of treatment. The median number of EDs was 63.5 in Study 1001 and 58.5 in Study 3002. For those subjects who continued into Study 3001, the median total exposure was 135.5 days. The extent of patient exposure meets the requirements of the EMA guideline.[16]

A summary of the incidence of adverse events (AE), serious adverse events (SAE) and so on across the 3 studies is presented in Attachment 2.

Important findings from the analysis of the safety data access the 3 studies include:

- The clinical evaluator states that the AEs observed in the submitted studies are generally consistent with that expected for a FVIII product. AEs observed commonly in the studies were non-specific that might commonly be observed in the general population (nasopharyngitis, arthralgia, headache, rash, cough and pyrexia). The proportion of such events assessed as being related to the drug was low.
- AEs and SAEs were more common in children than in adults. However, AEs assessed as being related to the drug were more common in adolescents and adults.

- The incidence of non-fatal serious AEs (SAEs) was found to be between 3.2% and 10.7% across the 3 studies.
  - *Study 1001*: non-fatal SAE incidence of 4.0%, with one event of hypersensitivity assessed as being related to rVIII-SingleChain.
  - *Study 3002*: non-fatal SAE incidence 10.7%, none assessed as being related to rVIII-SingleChain.
  - *Study 3001*: non-fatal SAE incidence of 3.2%, none of these events were assessed as being related to rVIII-SingleChain.
- The overall incidence of treatment-related adverse events (referred to as related 'Treatment Emergent Adverse Events' or 'related TEAE') was between 0.6% and 7.5%. This corresponded to a total of 21 AEs occurring in 15 subjects across the 3 studies:
  - *Study 1001*: Related TEAE incidence of 7.5% (total of 19 events in 13 patients)
  - *Study 3002*: Related TEAE incidence of 1.2% (total of 1 event in 1 patient)
  - *Study 3001*: Related TEAE incidence of 0.6% (total of 1 event in 1 patient).
- A total of 3 subjects withdrew due to AEs. Of these, one was assessed as related to rVIII-SingleChain (1 subject in Study 3001 with a hypersensitivity reaction).
- No cases of anaphylaxis were reported. However, a total of 4 events of 'hypersensitivity' or 'drug hypersensitivity' were reported across the 3 studies (2 adults, 1 adolescent and 1 child). The narratives of these events are presented in Attachment 2. All were considered related to rVIII-SingleChain. One event was assessed as 'serious' and involved severe hypersensitivity with pruritus, fever, erythema, headache, dyspnoea, chest discomfort, and rash occurring approximately 2.5 hours after an injection. 3 were assessed as 'non-serious' however details of these events were not provided (see clinical questions). One adult subject in Study 3001 discontinued treatment due to a hypersensitivity event. The remaining cases were able to continue treatment with antihistamine premedication.
- When considering any potential hypersensitivity or anaphylactic reaction TEAEs, the rate of events in Study 1001 was 8.6% (15 subjects with 20 events), the rate in Study 3002 was 15.5% (13 subjects with 19 events) and the rate in Study 3001 was 2.6% (4 subjects with 4 events). Although this data is non-specific, it provides a useful background to assist with interpretation of hypersensitivity reactions.
- The incidence of non-neutralising ADA in subjects who were negative at baseline and became positive after Baseline was 2.3% in Study 1001, 11.9% in Study 3002 and 0% in Study 3001. The clinical evaluator stated that the development of ADAs was not associated with any apparent increased risk of AEs or loss of efficacy. There were 14 subjects who developed ADAs and had PK data. According to the sponsor the PK profiles in these subjects were similar to those in subjects without ADAs.

Important negative findings of the safety analysis included the following:

- No subjects developed FVIII inhibitors in any of the 3 studies.
- No subjects developed antibodies against CHO cell proteins.
- Of the AEs that commenced during the surgical period of Study 1001, none were assessed as being related to rVIII-SingleChain.
- There were no thromboembolic events observed in the 3 submitted studies. One subject in Study 3002 developed an event of 'device occlusion' which was considered unrelated to the study drug.
- There were no deaths in the submitted studies.

- There were no serious hepatic adverse events reported in the 3 clinical studies. Analysis of liver function test (LFT) data was very limited. However, the clinical evaluator concludes that most subjects with abnormal LFTs appeared to have abnormal results at Baseline and/or were known to have hepatitis.
- Analysis of haematology laboratory data was very limited. However, the clinical evaluator concludes that clinically significant abnormalities appeared to be sporadic and infrequent.

Overall, the clinical evaluator concludes that the AE profile of rVIII-SingleChain is considered acceptable.

Clinical evaluator's recommendation

The clinical evaluator's views are presented in the first round clinical evaluation report (summarised under Clinical findings above and available as Attachment 2 to this AusPAR). The evaluator's view is that the benefit-risk balance of rVIII-SingleChain in the treatment of haemophilia A is favourable and the evaluator recommends that the application for registration of lonoctocog (Afstyla) be approved.

A second round clinical evaluation report was not completed for this submission, as only 3 targeted clarification questions were posed to the sponsor. These were satisfactorily addressed in the sponsor's responses.

Risk management plan

No outstanding issues were identified by the RMP evaluation.

Following the second round RMP evaluation, the sponsor submitted revised versions of the EU-RMP (version 3.1) and ASA (version 3.0). The only change to the Summary of Safety Concerns was that 'development of inhibitors' was changed from an important potential risk to an important identified risk.

The RMP evaluator found the proposed risk management plan to be acceptable. The additional pharmacovigilance activities include the ongoing Study 3001 and participation in EUHASS[23]. No additional risk minimisation activities are proposed.

The RMP evaluator suggests to implement EU-RMP (version 3.1, 5 December 2016, data lock point 28 August 2016) with Australian Specific Annex (version 3.0, 7 December 2016) and any future updates as a condition of registration.

Risk-benefit analysis

Delegate's considerations

Manufacturing and quality control

There are objections on quality grounds to the approval of lonoctocog alfa (Afstyla). These are summarised in the quality section of this report. Two main issues remain outstanding following the sponsor's responses:

1. *Regarding the specifications for the excipients histidine and polysorbate 80 which exceed the compendial requirements*: The sponsor stated in the response that they agree to tighten these specifications, as requested, in accordance with the Ph. Eur

[23] European Haemophilia Safety Surveillance system

01/2008:1643 Human coagulation factor VIII (rDNA) requirements. However the new specifications submitted in November 2016 do not meet the Ph. Eur requirement to be 80% to 120% of the stated content. The sponsor is requested to amend these specifications in accordance with the Ph. Eur 01/2008:1643 Human coagulation factor VIII (rDNA) requirements as agreed.

2. *Regarding approval of the proposed excursion during shipping:* The quality evaluator states that approval of the proposed excursion during shipping cannot be recommended. An application should be made post-approval in the form of a Category 3 application. In line with TGA Guidance document 14.4 Specific requirements on stability of biological medicines and Part 4.3 hours of the Minor Variation Guidelines, this application should provide data demonstrating that if the product is subjected to 18 hours at + 25°C on release, there are no downward trends evident during the remaining shelf life of 36 months at 2 to 8°C (worst case scenario) that would result in a product released at the lower end of the release specification not meeting end of shelf life specification.

In the Delegates opinion, after considering the issues identified in the quality evaluation reports and the TGA Product Summary Report, the Delegate agree with the quality evaluator that the proposed excursion during shipping cannot be approved at this stage. The sponsor is however requested to amend the specifications for the excipients histidine and polysorbate 80 in accordance with the Ph. Eur 01/2008:1643 Human coagulation factor VIII (rDNA) requirements.

Efficacy

The clinical development programme satisfactorily demonstrated the efficacy of rVIII-SingleChain in treatment, prophylactic treatment and peri-operative prophylaxis, for the prevention and control of bleeding in previously treated children, adolescents and adults with severe haemophilia A (FVIII < 1%).

In total, efficacy data based on the ITT population were available for 256 previously treated patients. This consisted of 160 adults, 14 adolescents (≥ 12 years to < 18 years) and 83 children (35 patients aged 0 years to < 6 years and 48 patients aged ≥ 6 years to < 12 years). For Study 3001, efficacy data based on the ITT population was available for prophylactic treatment in 146 patients, on demand treatment in 27 patents and surgical prophylaxis in 13 patients. In Study 3002, efficacy data was available for prophylactic treatment in 80 patients and on demand treatment in 3 patients.

It is not possible to formally compare efficacy between the on demand treatment group and prophylactic treatment group, because there was no randomisation into these arms and imbalance in baseline prognostic factors may bias the efficacy outcomes across arms.

The data demonstrated differences in efficacy, particularly in the ABR, for subjects aged < 6 years receiving prophylaxis (ABR 3.0 (95% CI: 2.3 to 4.0) compared to subjects aged ≥ 6 to < 12 years (ABR 7.4 (95% CI: 6.3 to 8.6)). Furthermore, clearance (based on per kg body weight) was higher in the paediatric population (0 to 12 years of age). These differences are expected to be managed by the individualisation of dosing in children.

Safety

The clinical development program has yielded sufficient safety data to permit registration of lonoctocog alfa (Afstyla). The safety profile seen in adults and children were considered by the clinical evaluator to be acceptable. The safety population covered a total of 412 subjects across the 3 studies.

No cases of inhibitor development were observed in the submitted studies of rVIII-SingleChain. As highlighted by the clinical evaluator, only previously treated patients at low risk of inhibitor development were enrolled in the submitted studies. This included exclusion of patients with a history or family history of inhibitors. A recent article in the

Lancet stated that in PUPs with severe haemophilia A, inhibitors form in approximately 30% of subjects, usually during the first 30 exposure days.[18] A recently published randomised trial demonstrated that the incidence of inhibitor development in PUPs is higher with recombinant products than with plasma derived products.[19] The EMA guideline recommends that a study of safety, efficacy and PK in PUPs should be commenced prior to a marketing authorisation of a novel FVIII product.[16] The sponsor is currently enrolling PUPs in an additional arm of Study 3001 (Arm 2) (as noted in the TGA RMP evaluation). An update to this study was provided by the sponsor in the response data following TGA questions. This stated that as of 28 August 2016, a total of 6 PUPs were enrolled in Arm 2 of the Study 3001 extension. At that time, there had been 1 case of inhibitor formation in a PUP (a 1 year-old boy). No cases of hypersensitivity reactions in any PUP were reported.

Although no cases of 'anaphylaxis' were reported, the narrative for the patient who experienced 'severe hypersensitivity' described severe symptoms, occurring within 2.5 hours of administration, which could have progressed to anaphylaxis. The sponsor's designation of this case as 'severe hypersensitivity' rather than 'anaphylaxis' was not provided (see *Clinical questions*), however this subject did continue in the trial with pre-medication. An additional 3 cases of 'hypersensitivity' or 'drug hypersensitivity' were reported which lacked further information, including the withdrawal of one patient due to hypersensitivity. 2 cases occurred in Study 1001 (n = 174), with a rate of 1.15%. In total, 4 cases from 412 subjects give a rate of approximately 0.97%. This appears higher than the rates listed in the current approved Summary of Product Characteristics (SmPC) for other similar products, where the rate of hypersensitivity is listed as either 'not known' or uncommon (≥ 1/1,000 to < 1/100) (see approved SmPC for Kovaltry and Advate).[24,25] These cases occurred on a background rate of all potential hypersensitivity or anaphylactic reaction treatment-emergent adverse events (regardless of relationship to the study drug) of between 2.6% and 15.5%. The rate was higher in children aged < 12 years. The correlation between the clinical safety data and the nonclinical finding of 'transient episodic body tremors' in almost all monkeys administered mid and high doses of lonoctocog alfa in a repeat-dose toxicity study, remains unexplained. However, the immunogenicity of lonoctocog alfa in monkeys is a major confounding factor for the interpretation of this finding.

In regards to risk minimisation for the risk of hypersensitivity, the sponsor has identified 'hypersensitivity' as a precaution in the draft PI document and identified 'life-threatening hypersensitivity reactions' as a contraindication. In addition, hypersensitivity is identified as a 'common' adverse reaction identified in clinical studies. However, the draft PI then states that hypersensitivity or allergic reactions have been observed 'rarely' with the use of FVIII products. It is important to note that EU RMP version 2.0 dated 8 July 2016 (Data Lock Point 28 August 2015) lists 'hypersensitivity and anaphylactic reactions' as an important identified risk. Furthermore, in the recent update to the EU RMP, an additional pharmacovigilance activity was added to further investigate the safety concern of 'Hypersensitivity/anaphylactic reactions' and 'development of inhibitors to factor VIII'. This activity is to participate in the EUHASS and provide interim updates based on EUHASS reports in each Periodic Safety Update Report (PSUR). In the Delegate's opinion, the current risk minimisation activities for the risk of hypersensitivity reactions are reasonable, however the statement in the PI that these reactions have been observed 'rarely' may mislead clinicians. This statement should be removed.

There is potential for misinterpretation of reported FVIII activity levels during monitoring of patients receiving Afstyla because the 2 available clinical assays report disparate

[24] European Medicines Agency. Summary of Product Characteristics (SmPC) for Advate.
[25] European Medicines Agency. Summary of Product Characteristics (SmPC) for Kovaltry.

results. The results determined by the OS assay are approximately 45% lower than those determined by the ChS assay. Lack of correction with a conversion factor to bring the results into alignment could lead to unnecessary additional doses, to higher chronic dosing (as in prophylactic therapy), or to unnecessary investigations for an inhibitor. In the Delegate's opinion, the statements in the draft PI document regarding this issue need to be strengthened.

Planned or ongoing studies

At the time of writing this overview, Study 3001 is ongoing with a projected submission date for the final Case Study Report as the fourth quarter of 2021. In addition, the sponsor has proposed to include interim updates from the EUHAUSS in each PSUR.

Summary of issues

Lonoctocog alfa is a form of rFVIII. It differs from endogenous FVIII in that a segment of the molecule (most of the B-domain and 4 amino acids of the adjacent a3 domain) has been removed. It is produced in CHO cells.

From the safety analysis of 412 subjects, a total of 4 cases of hypersensitivity reactions were identified in clinical trials. This rate of hypersensitivity reactions appears to be higher than that seen for similar agents (see discussion section, above).

Of the 6 previously untreated patients enrolled in an ongoing clinical trial, one case of inhibitor formation was reported.

The sponsor has proposed additional pharmacovigilance activities for the risks of hypersensitivity and inhibitor formation. These are in the form of one ongoing study (Study 3001) and participation in the EUHASS.

There is also potential for misinterpretation of reported FVIII activity levels during monitoring of patients receiving Afstyla because the 2 available clinical assays report disparate results. The sponsor proposes statements in the PI document to minimise this risk.

Overall risk-benefit

The Delegate agrees with the clinical evaluator that the benefit-risk balance is favourable for this product, in the population reflected by the sponsor's proposed indications.

Proposed action

The Delegate had no reason to say, at the time, that the application for Afstyla should not be approved for registration.

Questions for sponsor

1. Please provide an explanation for the exclusion of the 1500 IU and 2500 IU dose forms in the US.
2. Please clarify the distribution of age in each study group in Study 3002, particularly the distribution of the < 6 years group. The Clinical Study Report for Study 3002 provides mean, median, minimum and maximum age. However, the number of patients studied of each age is requested to assist with data interpretation.
3. Please amend the specifications for the excipients histidine and polysorbate 80 in accordance with the Ph. Eur 01/2008:1643 Human coagulation factor VIII (rDNA) requirements.
4. Please provide details of the 3 hypersensitivity or drug hypersensitivity reactions that were assessed as 'non-serious'. This detail should include the symptoms experienced,

timing of event and the definitions of 'mild', 'moderate' and 'severe' hypersensitivity reactions. Please also provide your definition of 'anaphylaxis' and explain why the case of 'severe hypersensitivity' did not meet the criteria for 'anaphylaxis'.

5. Please provide an updated analysis on the number of PUPs now enrolled in the Study 3001 extension and any available data on inhibitor development in these subjects.
6. Please provide an update on the current rate of hypersensitivity and anaphylactic reactions in Study 3001.

Request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. Can the committee comment on whether the current risk mitigation activities for the risk of hypersensitivity reactions are adequate? Does the committee have any additional comments or advice on this issue?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Questions for the sponsor

Question 1

> *'Please provide an explanation for the exclusion of the 1500IU and 2500IU dose forms in the US.'*

The clinical plan for CSL627 (rVIII-SingleChain) initially examined 5 presentation forms (dosage strengths): 250 IU, 500 IU, 1000 IU, 2000 IU and 3000 IU per vial.

Additional presentations of 1500 IU and 2500 IU were subsequently developed to help achieve an accurate bodyweight based patient dosing by combining as few as possible vials to avoid excess and wastage of reconstituted drug.

At the time of Biological License Application (BLA) submission to FDA in May 2015, the validation and stability package for submission of the additional CSL627 presentations was not available. The additional CSL627 presentations have now been submitted to FDA post-BLA approval and are currently under evaluation.

Question 2

> *'Please clarify the distribution of age in each study group in Study 3002, particularly the distribution of the < 6 years group. The Clinical Study Report for Study 3002 provides mean, median, min and max age. However, the number of patients studied of each age is requested to assist with data interpretation.'*

As requested, the age distribution of subjects (safety population) in Study 3002 is provided in Table 9.

Table 9. Study 3002 Demographics by Age (Safety Population)

Age	Number of Subjects	Percent (%)
1	2	2.4
2	10	11.9
3	3	3.6
4	10	11.9
5	10	11.9
6	6	7.1
7	7	8.3
8	9	10.7
9	8	9.5
10	5	6.0
11	14	16.7
TOTAL	**84**	

Question 3

> *'Please amend the specifications for the excipients histidine and polysorbate 80 in accordance with the Ph. Eur 01/2008:1643 Human coagulation factor VIII (rDNA) requirements.'*

As requested, the specifications for the excipients histidine and polysorbate 80 have been amended in accordance with the Ph. Eur 01/2008:1643 Human coagulation factor VIII (rDNA) requirements and the relevant CTD sections have been updated.

Question 4

> *'Please provide details of the 3 hypersensitivity or drug hypersensitivity reactions that were assessed as 'non-serious'. This detail should include the symptoms experienced, timing of event and the definitions of 'mild', 'moderate' and 'severe' hypersensitivity reactions. Please also provide your definition of 'anaphylaxis' and explain why the case of 'severe hypersensitivity' did not meet the criteria for 'anaphylaxis'.'*

Cumulatively in Afstyla clinical Studies 1001, 3002, and 3001, there have been a total number of 258 subjects who have received at least 1 dose of Afstyla as of 29 May 2015. There were 4 subjects who experienced hypersensitivity reactions in these clinical studies. 1 of these subjects experienced a serious event. The remaining 3 subjects experienced non-serious events. To date, there have been no subjects with a report of anaphylaxis or anaphylactic reaction. Thus, the overall frequency of subjects with the event of hypersensitivity reported in all Afstyla clinical studies is 1.6% (4 subjects in 258 total subjects).

All available information outlining pertinent details of the hypersensitivity reactions about the 3 subjects who developed non-serious reactions is provided below. Limited information about symptoms/signs was provided by investigators for these non-serious cases.

Assessments of whether the hypersensitivity reactions were mild, moderate, and severe were made by the investigator, according to their medical judgment. Although not specific to hypersensitivity reactions, the guidance in Table 10 was provided in the protocol for investigators to assess the severity of adverse events.

Table 10. Severity descriptions for adverse events

Severity	Definition
Mild	A type of AE that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	A type of AE that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Severe	A type of AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

CDISC SDTM Severity Intensity Scale for Adverse Event Terminology

Non-serious hypersensitivity cases are as follows:

1. Non-serious AE of drug hypersensitivity: A 55 year old White male who developed non-serious event of drug hypersensitivity 1 hour after study medication, with 2 positive rechallenges (approximately 10 days later), 1 hour after study medication, and 10 days after study medication administration), all with mild and moderate intensity. The patient had general symptoms. The patient had high pressure in chest, problem with breathing and feeling hot. Each time, after taking Afstyla, the symptoms became stronger. Usually, the symptoms resolved after 24 hours. The subject fully recovered and none were associated with any reported local reaction. Afstyla administration was discontinued and the subject was withdrawn from the study on 14 May 2015 after second rechallenge. Of note, no pre-medication with antihistamines or steroids was applied prior to Afstyla administration for all occurrences.
2. Related non-serious TEAE of hypersensitivity (on 2 separate occasions): A 32 year old Asian male who developed 2 non-serious hypersensitivity reactions, the first approximately 9 hours after study medication administration, and the second 70 minutes after study medication. The dose of study drug was unchanged for both events. The subject recovered from both events. The first hypersensitivity event was mild in intensity, non-serious, and did not require a change in study medication. The event was an isolated case and resolved on the same day that it had started. The second event of hypersensitivity occurred 3 days after the subject's first injection, and was also mild. The subject continued Afstyla treatment without recurrence of any hypersensitivity event. Of note, no pre-medication was used.
3. Related non-serious treatment emergent AE of hypersensitivity (mild): A 9 year old Asian male subject with a history of bronchial asthma and conjunctivitis, who had a pre-existing inhibitor, developed a non-serious event of hypersensitivity reaction, 18 minutes after study medication administration. The event resolved, and the subject continued treatment with Afstyla without pre-medication and with no further hypersensitivity event.

Serious hypersensitivity case:

1. A 17 year old Asian male with a history of hypersensitivity was reported to have a serious AE of hypersensitivity reaction. The subject was assigned to a prophylaxis regimen at a dose of 43 IU/kg. Of note, this patient had a prior history of hypersensitivity as follows: hypersensitivity to cryoprecipitates, local hypersensitivity

with leucoplast brand of plaster and extrinsic asthma. The subject also reported a previous history of acute tonsillopharyngitis, upper respiratory tract infection with laryngitis, pharyngitis and tonsillitis. The patient developed fever 2 to 3 hours post infusion at 01:00 in the morning. Upon waking up, he felt severe pruritus. At 09:30 am, he experienced difficulty of breathing and noticed his hands and arms to be red. He also developed severe headache. The patient went to the hospital (study site). Upon physical examination in the emergency room, the patient was awake, comfortable, with no pallor, no cyanosis, no wheezing, no rales, clear breath sounds and no organomegaly. Upper extremities were erythematous, blanching (with maculopapular rashes on both upper extremities, blanching). Lower extremities-no rashes; full pulses. At the emergency department, the patient was nebulised with Combivent, 1 dose. Also given hydrocortisone 250 mg IV and Diphenhydramine 50 mg IV. His dyspnoea improved and rashes diminished. Patient was discharged on the same day around noon with Prednisone and Iterax. At 18:15, the patient was called and reported that condition improved completely. The subject did not experience a subsequent reaction to the study medication following an observed dose and continued in the study with no sequelae.

The sponsor's pharmacovigilance experts reviewed and discussed all events of potential hypersensitivity reactions, including the serious case of hypersensitivity against published criteria of anaphylaxis (as defined below).

- Anaphylaxis definition: Anaphylaxis is a potentially life threatening, severe allergic reaction, that must be treated as a medical emergency, usually with rapid administration of subcutaneous epinephrine. It is an acute allergic response involving immunoglobulin E subtype mediated, antigen stimulated mast cell activation resulting in histamine release. Reaction may begin within minutes or even seconds of exposure, and rapidly progress to cause airway constriction, skin and intestinal irritation, and altered heart rhythms. In severe cases, it can result in complete airway obstruction, shock, and death. Symptoms of anaphylaxis are potentially life threatening and include any one of the following:
  - Difficult/noisy breathing
  - Swelling of tongue
  - Swelling/tightness in throat
  - Difficulty talking and/or hoarse voice
  - Wheeze or persistent cough
  - Persistent dizziness and/or collapse
  - Pale and floppy (in young children)

The hypersensitivity reaction experienced by [the subject with severe hypersensitivity] does not appear to meet criteria of anaphylaxis for the following reasons:

- On physical examination, the subject was awake, comfortable, with no pallor, no cyanosis, no wheezing, no rales, and clear breath sounds. Thus, there was no evidence of respiratory distress.
- The subject did not have typical severe symptoms of anaphylaxis (that is, tongue swelling, throat tightness, wheezing, loss of consciousness, and so on).
- Event latency was 2 to 3 hours, with respiratory symptoms appearing 10.5 hours later (that is, there was no rapid onset and progression of signs/symptoms that is typical of anaphylactic reactions).

- Event did not reoccur and therefore an immunoglobulin E subtype mediated response is unlikely.

In conclusion, the only subject in clinical trials to date with a serious hypersensitivity reaction did not meet criteria for anaphylaxis, and continued to be treated with study medication. The rest of the subjects who reported hypersensitivity reactions were determined to be of mild to moderate nature and non-serious by the investigator.

Question 5

> *'Please provide an updated analysis on the number of PUPs now enrolled in the Study 3001 extension and any available data on inhibitor development in these subjects.'*

Currently there are 12 PUPs enrolled in the ongoing CSL627-3001 study. A total of 3 PUPs have been diagnosed with a low titre inhibitor. The median exposure day at diagnosis was 20 (range 12 to 32). All subjects have been assigned an intensified prophylactic regimen and remain on study.

Question 6

> *'Please provide an update on the current rate of hypersensitivity and anaphylactic reactions in Study 3001.'*

As of 28 August 2016 data cut off, there has been 1 subject with non-serious events of hypersensitivity, no serious hypersensitivity reactions, and no anaphylaxis reported in Study 3001. The rate of hypersensitivity reactions in Study 3001 as of 28 August 2016, was 0.4% (1 subject out of 228 total).

Manufacturing and quality control decision and issues

Regarding approval of the proposed excursion during shipping:

The sponsor acknowledges that the proposed excursion during shipping cannot be recommended and that an application will be made post-approval in the form of a Category 3 application in the event of a temperature excursion during shipment.

Advisory committee considerations

The Advisory Committee on Medicines (ACM), taking into account the submitted evidence of efficacy, safety and quality, considered Afstyla lyophilised powder containing 250, 500, 1000, 1500, 2000, 2500 and 3000 IU of lonoctocog alfa, and are of the opinion that there is an overall positive benefit–risk profile for the indication:

> *'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.'*

Proposed conditions of registration

The ACM agreed with the Delegate on the proposed conditions of registration.

The ACM advised the following in response to the Delegate's specific questions on this submission:

Specific advice

1. *Can the committee comment on whether the current risk mitigation activities for the risk of hypersensitivity reactions are adequate?*

The ACM advised that lonoctocog alfa was well tolerated and that the risk mitigation activities are adequate.

2. *Does the Committee have any additional comments or advice on this issue?*

The ACM considered that inhibitor production in previously untreated patients was adequately covered in the PI but queried whether the Canadian statement might be usefully added to the indication.

The ACM noted that discrepancies between laboratories in monitoring between the OS and ChS assays.

The ACM advised that implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Afstyla lonoctocog alfa (recombinant single-chain coagulation factor VIII) 250 IU, 500 IU, 1000 IU, 1500 IU, 2000 IU, 2500 IU and 3000IU powder for injection indicated for:

> *'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.'*

Specific conditions of registration applying to these goods

- The Afstyla EU-RMP (version 3.1, 5 December 2016, data lock point 28 August 2016) with Australian Specific Annex (version 3.0, 7 December 2016) and any future updates as agreed with the TGA will be implemented in Australia.
- Batch Release Testing and Compliance with Certified Product Details (CPD)
  - It is a condition of registration that all batches of Afstyla lonoctocog alfa (rch), powder (and solvent) for injection imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
  - It is a condition of registration that each batch of Afstyla lonoctocog alfa (rch), powder (and solvent) for injection imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.

This batch release condition will be reviewed and may be modified on the basis of actual batch quality and consistency. This condition remains in place until you are notified in writing of any variation.

The sponsor must supply:

- Certificates of Analysis of all active ingredient (drug substance) and final product.

- Information on the number of doses to be released in Australia with accompanying expiry dates for the product and diluents (if included).
- Evidence of the maintenance of registered storage conditions during transport to Australia.
- 5 containers of each batch for testing by the TGA Laboratories Branch together with any necessary standards, impurities and active pharmaceutical ingredients (with their Certificates of Analysis) required for method development and validation.

Attachment 1. Product Information

The PI for Afstyla approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

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