



Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for efmoroctocog alfa¹ (rhu)

Proprietary Product Name: Eloctate

Sponsor: Biogen Idec Australia Pty Ltd

January 2015

TGA Health Safety
Regulation

¹ The non-proprietary name has changed post registration from efralococog alfa to efmoroctocog alfa to harmonise with the International Non-proprietary Name.

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 <<http://www.tga.gov.au>>.

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- 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, in that it will provide 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.

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List of the most common abbreviations used in this AusPAR

Abbreviation	Meaning
aPTT	activated partial thromboplastin time
ABR	annualised bleeding rate
ACPM	Advisory Committee for Prescription Medicines
ACSOM	Advisory Committee on the Safety of Medicines
AE	adverse event
AHCDO	Australian Haemophilia Centre Directors' Organisation
APC	activated protein C
ARTG	Australian Register of Therapeutic Goods
AUC	area under the concentration-time curve
BU	Bethesda unit
CER	Clinical evaluation report
CHO	Chinese hamster ovary
CI	confidence interval
C _{max}	maximum plasma activity
CMI	consumer medicine information
CSR	clinical study report
DFU	directions for use
EC ₅₀	50% effective concentration
ECG	electro cardio gram
ED	exposure day
EMA	European medicines agency
FcRn	neonatal Fc receptor
FVIII	coagulation factor VIII
GCP	Good clinical practice

Abbreviation	Meaning
GLP	Good laboratory practice
h	hour(s)
HC HBV	hepatitis B virus
HCV	hepatitis C virus
Hem A mice	Factor FVIII deficient mice
HIV	human immunodeficiency virus
HR	heart rate
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IgG	immunoglobulin G
IgG1	immunoglobulin G1
ISTH	the International Society on Thrombosis and Haemostasis
ITI	immune tolerance induction
IU	international unit
IV	intravenous
KO	knock out
LC	light chain
MRT	mean residence time
NBA	National Blood Authority
PI	product information
PK	Pharmacokinetic/s
PT	prothrombin time
PTP	previously treated patient
PUP	previously untreated patient
QoL	quality of life
RBC	red blood cells

Abbreviation	Meaning
rFVIII	recombinant coagulation factor VIII
rFVIIIFc	recombinant coagulation factor VIII Fc fusion protein
RMP	risk management plan
SAE	serious adverse event
SD	standard deviation
$t_{1/2}$	half-life
TGA	Therapeutic Goods Administration
Time 1%	time after dose when FVIII activity has declined to 1 IU/dL above baseline
Time 3%	time after dose when FVIII activity has declined to 3 IU/dL above baseline
URTI	upper respiratory tract infection
vWF	von Willebrand factor
WFI	water for injection
WHO	World Health Organisation

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	New biological entity
<i>Decision:</i>	Approved
<i>Date of decision:</i>	18 June 2014
<i>Active ingredient:</i>	Efmoroctocog alfa (rhu ²) ³
<i>Product name:</i>	Eloctate
<i>Sponsor's name and address:</i>	Biogen Idec Australia Pty Ltd Suite 1, Level 5 123 Epping Rd North Ryde, NSW 2113
<i>Dose form:</i>	Powder for injection and diluent
<i>Strengths:</i>	250 international units (IU), 500 IU, 750 IU, 1000 IU, 1500 IU, 2000 IU and 3000 IU
<i>Containers:</i>	Type I glass vial (powder) and pre-filled syringe (diluent)
<i>Pack size:</i>	Single
<i>Approved therapeutic use:</i>	<p><i>Eloctate is a long-acting antihaemophilic factor (recombinant) indicated in adults and children (≥ 12 years) with haemophilia A (congenital factor VIII deficiency) for:</i></p> <ul style="list-style-type: none"> • <i>control and prevention of bleeding episodes</i> • <i>routine prophylaxis to prevent or reduce the frequency of bleeding episodes</i> • <i>perioperative management (surgical prophylaxis)</i> <p><i>Eloctate does not contain von Willebrand factor, and therefore is not indicated in patients with von Willebrand's disease.</i></p>
<i>Route of administration:</i>	Intravenous (IV) infusion
<i>Dosage:</i>	Refer to the Product Information (PI; Attachment 1)
<i>ARTG numbers:</i>	210521 (250 IU), 210519 (500 IU), 210523 (750 IU), 210525 (1000 IU), 210522 (1500 IU), 210524 (2000 IU), 210520 (3000 IU).

² recombinant human

³ The ingredient name at the time of submission and registration was Efralococog alfa, The name was subsequently changed on 20 February 2015 to harmonise to the International Non-proprietary Name (INN) Efmoroctocog alfa. The AusPAR document has been amended by replacing the previous name efralococog alfa with approved INN efmoroctocog alfa.

Product background

Haemophilia is an inherited, X chromosome-linked bleeding disorder. In Australia there are approximately 2,600 people with haemophilia and nearly all are male. Haemophilia A is the most common form and is due to the deficiency of factor VIII. Reduced blood coagulation results in bleeding which is most commonly internal, usually into the joints or muscles. Over time, recurrent bleeds can cause permanent damage such as arthritis, chronic pain and joint damage requiring surgery.

Efmoroctocog alfa (rhu) is a recombinant factor VIII (rFVIII) product that increases plasma factor VIII levels as a temporary correction of the bleeding tendency in haemophilia A.

This AusPAR describes the application by Biogen Idec Australia Pty Ltd (the sponsor) to register Eloctate (efmoroctocog alfa (rhu)) powder for injection, 250 IU, 500 IU, 750 IU, 1000 IU, 1500 IU, 2000 IU and 3000 IU for the following indication:

Eloctate is a long-acting antihaemophilic factor (recombinant) indicated in adults and children (≥ 12 years) with haemophilia A (congenital factor VIII deficiency) for:

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

Eloctate does not contain von Willebrand factor, and therefore is not indicated in patients with von Willebrand's disease.

The TGA Delegate of the Secretary designated recombinant human coagulation factor VIII Fc fusion protein as an orphan drug *for the control and prevention (including routine prophylaxis) of bleeding episodes in adults and children with haemophilia A* on 23 February 2013.

Regulatory status

The product received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 27 June 2014.

At the time this application was considered by the TGA, similar applications were under consideration in USA, (March 2013), Canada (July 2013), South Africa (October 2013), and Japan (January 2014). Submissions were proposed for New Zealand (2014) and European Union (EU) European Medicines Agency (EMA) (2014).

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <<https://www.tga.gov.au/product-information-pi>>.

II. Quality findings

Introduction

Currently registered rFVIII products in Australia include;

- Kogenate FS (octocog alfa) (full-length FVIII; baby hamster kidney (BHK) cells; “2nd-generation”)

- Advate (octocog alfa) (full-length FVIII; Chinese hamster ovary (CHO) cells; “3rd-generation” i.e. no added human or animal proteins in manufacture)
- Xyntha (moroctocog alfa) (B domain deleted; CHO cells; “3rd-generation”)
- NovoEight (turoctocog alfa) (truncated B domain; CHO cells; “3rd-generation”)

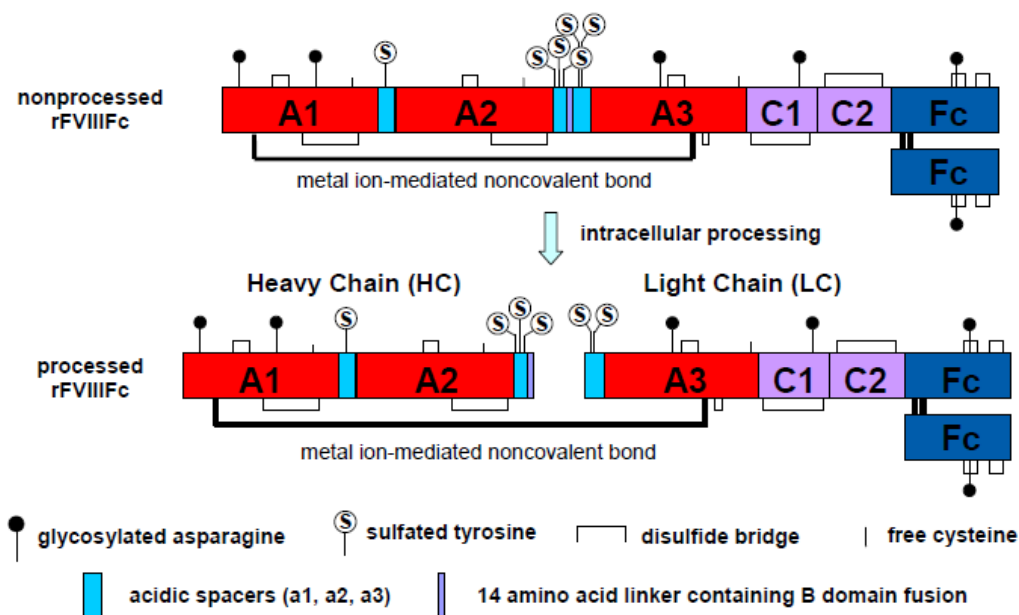
Eloctate is a new generation of rFVIII product; a B domain deleted FVIII linked to the Fc portion of Immunoglobulin G (IgG) and is produced in a human cell line.

Drug substance (active ingredient)

Structure

Recombinant coagulation factor VIII Fc fusion protein (rFVIII Fc) is a fully recombinant fusion protein consisting of a single molecule of B domain deleted human coagulation factor VIII (FVIII) covalently linked to the dimeric Fc domain of human immunoglobulin G1 (IgG1) with no intervening sequence. rFVIII Fc is produced in human embryonic kidney (HEK) cells. rFVIII Fc is a heterodimer comprised of FVIII Fc single chain and Fc single chain associated through disulphide bonds at the hinge regions of the Fc fragments as well as extensive non covalent interactions between the Fc fragments. rFVIII Fc confers the pro-coagulation function of clotting factor VIII for effective haemostasis. The presence of the Fc domain enables rFVIII Fc to bind to the neonatal Fc receptor (FcRn), which protects Fc containing molecules from catabolism and extending their plasma half-life.

Figure 1. Schematic diagram of rFVIII Fc structure.



During culture, the majority of the FVIII moiety is processed intracellularly to generate an approximately 90 kDa FVIII heavy chain and an approximately 130 kDa FVIII light chain Fc fusion (LC-Fc). The FVIII heavy chain remains associated to the LC-Fc through metal ion dependent non covalent interactions.

Manufacture

One cell bank vial is used to produce one discrete batch of rFVIII Fc drug substance. It is prepared at the bioreactor scale using media that are free of animal derived components.

Cell banking processes are satisfactory. All viral and prion safety issues have been addressed for the fermentation and purification processes.

Physical and chemical properties

The majority of rFVIII Fc is cleaved intracellularly. The non-cleaved single chain form, referred to as single chain rFVIII Fc (SCrFVIII Fc) The SCrFVIII Fc was isolated and extensively characterised and is active and generally comparable to the processed form, and is considered a product related substance.

rFVIII Fc activity was assessed using the FVIII coagulation assay based on activated partial thromboplastin time (aPTT), the FVIII chromogenic assay, and an FcRn binding assay. In addition a number of functional characterisation assays were conducted on rFVIII Fc drug substance. The primary structure agreed with the predicted amino acid sequence. Sites of glycosylation were confirmed by peptide mapping. rFVIII Fc post translational modifications include N linked glycosylation sites, sulphated tyrosine residues, and removal of the lysine residues at the C termini of both peptide chains.

Specifications

Appropriate validation data have been submitted in support of the test procedures for the proposed specifications, which control identity, content, biological activity (potency), purity and other biological and physical properties of the drug substance relevant to the dose form and its intended clinical use.

Stability

Real time data support the shelf life for the drug substance of 1 year at -70°C.

Drug product

The rFVIII Fc drug product is a sterile, non pyrogenic, single use, preservative free, white to off white, lyophilized powder for injection for IV infusion in a single use vial. Each vial contains nominally 250 IU, 500 IU, 750 IU, 1000 IU, 1500 IU, 2000 IU or 3000 IU of rFVIII Fc and is presented in a kit containing a vial adaptor and a prefilled diluent syringe with 3 mL of sterile water for injection (WFI).

The rFVIII Fc drug product is lyophilised in a Type I glass vial closed with a teflon coated chlorobutyl stopper and sealed with a 20 mm aluminium flip off crimp seal, with different colours used for different dose strengths.

The product is reconstituted for use by connecting the prefilled diluent syringe and the product vial using the vial adaptor. The diluent is then added to the powder and the product allowed to dissolve (clear instructions are provided regarding not to shake). Once dissolved the product is returned to the syringe and used as soon as possible. In use data supports the storage of resuspended product as described in the PI.

Manufacture

Information was evaluated on the manufacturing process, including sterilisation, lyophilisation and filtration steps.

Specifications

The proposed specifications, which control identity, potency, purity, dose delivery and other physical, chemical and microbiological properties relevant to the clinical use of the product have been evaluated.

The same specifications are applied for all the drug product strengths except for protein concentration, quantity of rFVIII Fc per vial (as measured by chromogenic coagulation activity assay), and endotoxin.

Stability

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. The product is not photostable and should be protected from light. The lyophilised product is stable when frozen. The diluent syringe must not be frozen and as they are supplied in the same package, the storage conditions are stipulated on the packaging.

The recommended shelf life is 12 months when stored at 2°C to 8°C which is less than that proposed by the sponsor. There was insufficient data to support the storage of the product for 6 months at room temperature. No variations in storage temperature during shipping have been approved.

In use stability data support the in use conditions described in the PI.

Labelling, packaging and documentation

Updated labelling, packaging and PI documents were provided in response to requests from TGA for revisions to quality aspects and are considered acceptable.

Quality summary and conclusions

The administrative, product usage, chemical, pharmaceutical and microbiological data submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

The use of Schott vials has not been supported by sufficient data and at this stage is not recommended for approval (the approved vials are manufactured by Nipro).

The module 3 (quality) evaluators recommended that Eloctate (efmoroctocog alfa (rhu)) 250 IU, 500 IU, 750 IU, 1000 IU, 1500 IU, 2000 IU and 3000 IU powder for injection vial plus diluent syringe should be approved with the inclusion of specific registration conditions relating to batch release, testing and certified product details. Details of these conditions are beyond the scope of the AusPAR.

III. Nonclinical findings

Introduction

General comments

The quality of the nonclinical studies was generally satisfactory with most studies performed according to good laboratory practice (GLP) principles and protocols were consistent with the International Conference on Harmonisation of Technical Requirements

for Registration of Pharmaceuticals for Human Use (ICH) guideline for biotechnology-derived therapeutic products (ICH S6⁴). All animal studies used the clinical route (IV administration). The nonclinical testing strategy focussed on the extended elimination half-life of rFVIII Fc relative to existing registered recombinant FVIII products (for example, Advate and Xyntha/ReFacto), with a number of primary pharmacology and pharmacokinetic (PK) studies that compared clotting times and activity. These studies demonstrated pharmacological responsiveness to rFVIII Fc in all tested species, including the rat and cynomolgus monkey, which were used in the GLP repeat dose toxicity studies. Determination of safety pharmacology parameters were incorporated into the repeat dose toxicity studies. All repeat dose toxicity studies also monitored antibody development. Local tolerance was assessed in the repeat dose toxicity studies.

Comparability of manufactured batches

Information on the commonality of the manufactured batches used in the nonclinical studies to those used in clinical studies was provided. These batches demonstrated comparable clotting activities/efficacies, PK profiles and tolerance potentials. Studies used either the frozen liquid formulation of rFVIII Fc or the lyophilised forms. Of the two lyophilised formulations, the former was used in Phase III clinical studies as well as the second GLP monkey study, and the latter, proposed as the commercial use product, was examined in an immunogenicity study in FVIII deficient (Hem A) mice.

Pharmacology

Primary pharmacology

Studies using surface plasmon resonance techniques demonstrated binding of rFVIII Fc to mouse, rat, cynomolgus monkey and human Fc receptor (FcRn) (affinities calculated as 50% effective concentration (EC₅₀): mouse 11.7 nM, rat 10.7 nM, monkey 52.1 nM, human 51.7 nM). The association between the Fc moiety and FcRn is the probable mechanism for the prolonged circulating half-life of rFVIII Fc⁵. Affinity of rFVIII Fc for von Willebrand Factor (vWF) was comparable to that of the registered recombinant FVIII product, Xyntha. Similarly, thrombin mediated dissociation of rFVIII Fc from vWF was similar to that of Xyntha and cleavage/activation of rFVIII Fc by thrombin, generated similar by products as the recombinant FVIII comparator (rFVIII), ReFacto. The ability of rFVIII Fc to form the tenase complex with activated Factor IX was similar to ReFacto and similarly, activated protein C (APC) inactivated rFVIII Fc to a similar degree as ReFacto.

In vivo acute and prophylactic efficacy of rFVIII Fc was demonstrated in (Hem A) mice. Clotting activity of rFVIII Fc, measured by a FVIII specific chromogenic assay, was detected at up to 72 hours post dose, whereas activities of equal doses of either rFVIII products ReFacto or Advate were below the level of quantification by 48 hours post dose, consistent with the longer elimination half-life (t_{1/2}) of rFVIII Fc than ReFacto or Advate. Acute efficacy, assessed by measuring blood loss sustained following injury in Hem A mice, treated with rFVIII Fc or rFVIII (Advate), was similar between the two FVIII products. Different manufactured batches of rFVIII Fc demonstrated dose dependent reduction of blood loss following injury. Prophylactic protection in Hem A mice was more effective with rFVIII Fc than rFVIII (Advate), whereby all mice that received rFVIII Fc survived injury (tail vein transection) and rates of re bleeding were significantly lower in this group than in mice that received Advate, which also had lower survival rates (approximately 50%).

⁴ EMA/CHMP/ICH/731268/1998 ICH guideline S6 (R1) - preclinical safety evaluation of biotechnology-derived pharmaceuticals.

⁵ The abbreviation rFVIII-Fc was used by the non-clinical evaluator and has been replaced in the text with rFVIII Fc for consistency.

The activities of rFVIII Fc drug substance, purified processed rFCVIII Fc and SCrFVIII Fc were compared by the chromogenic and the aPTT assays. SCrFVIII Fc activity was lower than purified processed rFVIII Fc and rFVIII Fc drug substance, when activity was assessed by the aPTT assay or by monitoring thrombin generation, whereas the chromogenic assay findings did not reveal differences in activities among the different forms. Further, rFVIII Fc specific activity (assessed by aPTT) was approximately 10% lower than purified processed rFVIII Fc, suggesting a minor influence of SCrFVIII Fc in the total activity of rFVIII Fc drug product. In Hem A mice, prophylactic efficacy was comparable between SCrFVIII Fc and rFVIII Fc drug substance, in which survival rates and re-bleeding events were similar between the two forms of rFVIII Fc⁶.

Secondary pharmacodynamics and safety pharmacology

Since rFVIII Fc is intended as a replacement therapy to restore deficiencies in endogenous FVIII to normal levels, secondary pharmacology studies were not essential. With regard to safety pharmacology studies, cardiovascular systems (heart rate (HR) and electro-cardio gram (ECG)) were part of the protocols for the two pivotal 4 week rat and monkey studies. However, ECG findings were confined to narrative assurances by a veterinary pathologist who inspected the waveform readings. No other organ systems were investigated. Nevertheless, there were no overt adverse findings to indicate specific effects on organ systems and its use as a replacement for an endogenous substance would suggest a low risk of targeted toxicity. Therefore, in view of the product type, the absence of safety pharmacology studies is not considered to be a deficiency.

Pharmacokinetics

PK parameters were determined from single dose studies in mice, rats, dogs and monkeys and repeat dose toxicity studies in rats and monkeys.

Relative to non Fc subunit containing rFVIII comparators, rFVIII Fc displayed prolonged elimination $t_{1/2}$ and higher area under the concentration-time curve (AUC) in mice, rats and dogs. The $t_{1/2}$ for rFVIII Fc and rFVIII (Xyntha) were indistinguishable in mice lacking the FcRn receptor, whilst overexpression of the FcRn receptor resulted in higher $t_{1/2}$ and AUC for rFVIII Fc, confirming that its prolonged activity is dependent on its interaction with the FcRn receptor. For reasons that were not clear, the $t_{1/2}$ and AUC of rFVIII Fc and Xyntha were comparable in monkeys. In vitro FcRn binding assays showed comparable binding of rFVIII Fc to human and monkey FcRn (EC_{50} approximately 50 nM) and greater binding to mouse and rat FcRn (EC_{50} approximately 10 nM). Relatively long $t_{1/2}$ was observed in patients (clinical overview).

In a tissue distribution study, iodinated (¹²⁵I) rFVIII Fc was administered to Hem A mice and double knock out (KO) mice (FVIII/vWF KO) and distribution was monitored by quantitative whole body radiographic analysis. High levels were detected in highly perfused organs such as liver, lungs, kidneys and spleen. Tissue radioactivity levels were significantly lower in the Hem A mice than in double KO mice. The elimination $t_{1/2}$ was approximately 2 hours in double KO mice compared to 8 hours in Hem A mice. In particular, high levels of radioactivity (relative to blood) were noted in liver and bile of double KO mice compared to Hem A mice.

Overall, as with clinical findings, prolonged $t_{1/2}$ and slower clearance relative to non Fc subunit containing comparators were notable features of the PK profile of rFVIII Fc in all tested animals except monkeys. As well, the development of neutralising anti rFVIII Fc

⁶ The text of this paragraph has been slightly amended from the original for clarity.

antibodies resulted in lower exposures after repeat dosing, limiting the utility of repeat dose toxicity studies in animal species.

Toxicology

Acute toxicity

A single dose toxicity study to determine dose tolerance was conducted in cynomolgus monkeys. Maximum tested dose rFVIII Fc was 20,000 IU/kg IV, with a seven day observation period, in which no significant clinical signs or gross pathological findings were noted. Haematological parameters at up to 16 hours post dose were also monitored in which shortened aPTT (but not prothrombin time (PT)) was observed, while platelet and fibrinogen levels were not altered. Overall, rFVIII Fc was well tolerated in the monkey and displayed a low order of acute toxicity by the IV route.

Repeat dose toxicity

Four repeat dose toxicity studies were performed and assessed the chronic effects of rFVIII Fc in rats and monkeys. With the exception of one non GLP pilot study in monkeys, all other studies, using the IV route, were for 4 weeks and included protocols for measuring antibodies that developed over the course of the treatment period. Studies were generally consistent with ICH guideline requirements; however, due to the development of antibodies, duration of the studies was short for a chronic use product. In fact, in one of the monkey studies there were profound impairments of haemostatic function as a result of antibody development which neutralised endogenous FVIII (acquired haemophilia) and affected survival of test animals. Dosing regimen used in the animal studies was every second day (compared to clinical use of every 3 to 5 days for routine prophylaxis and every 12 to 48 hours for the control and prevention of bleeding episodes). It was noted also that the formulation of rFVIII Fc used in these studies included a different drug substance batch from the batch used in clinical trials and intended for registration. However, the batch in the other monkey study was also the drug product formulation used in a Phase III and an extension clinical study.

Relative exposure

Plasma exposures (as maximum plasma activity (C_{max}) and AUC) ascertained from the repeat dose toxicity studies are compared with human exposures in Table 1 below. Day 1 PK parameter values were used, since blood FVIII levels dropped considerably with repeated dosing because of the development of neutralising antibodies. Relatively high exposures were achieved in rat and monkey studies: C_{max} (exposure ratios up to 8 in rats and 26 in monkeys); and AUC (exposure ratios up to approximately 20 in rats and 140 in monkeys). However, since neutralising antibodies to rFVIII Fc affected levels of exposure to the test article, potential toxicities were likely to be minimised in the repeat dose studies. Indeed, the reported adverse effects in these studies were secondary to changes associated with the effect of neutralising antibodies on endogenous FVIII. For this reason, the relatively high exposure ratios that were derived (as either C_{max} or AUC comparisons) may not adequately reflect the true safety margin of rFVIII Fc relative to clinical dosing.

Table 1: Exposures in 4 week repeat-dose toxicity studies.

Species Study No. [Test batch potency]	Study duration	Dosing regime n	Dose (IU/kg)	C _{max} (µg/mL) [as IU/mL*]	AUC _{0-∞} (µg.h/mL) [as IU.h/mL*]	RE [^] (C _{max})	RE [^] (AUC)
Rat (SD) CN53610 [8548 IU/mg]	4 weeks (Day 1 values)	Every second day	50	0.07 [0.6]	1.04 [8.9]	0.5	3.2
			250	0.42 [3.6]	3.5 [29.9]	3	10.7
			1000	1.09 [9.3]	6.3 [53.9]	7.8	19.3
Monkey (Cynomol gus) CN53056 [8549 IU/mg]	4 weeks (Day 1 values)	Every second day	50	0.14 [1.2]	2 [17.1]	1	6.1
			250	0.8 [6.8]	10.8 [92.3]	5.7	33
			1000	2.8 [23.9]	37.5 [320.6]	20	115
Monkey (Cynomol gus) N110486 [8262 IU/mg]	4 weeks (Day 1 values)	Every second day	50	0.16 [1.3]	2.3 [19]	1.1	6.8
			250	0.88 [7.3]	12.1 [100]	6.1	35.7
			1000	3.8 [31.4]	48 [396.6]	26.4	142
Human 997HA101	-	65	50	[1.19]	[2.8]	-	-

[^]Relative exposure, Animal C_{max} or AUC/Clinical C_{max} or AUC; Mean of male and female values are shown;
* converted to IU/mL or IU.h/mL based on potency of batch used in the study.

Major toxicities

Repeated doses of rFVIII^{IFc} were generally well tolerated by both animal species used, with no overt and targeted toxicities noted. Clinical signs were minimal with incidences of swelling and discolouration noted in hindlimbs and forelimbs of treated monkeys. These effects were likely to be a consequence of impaired haemostasis due to neutralising antibodies and trauma from blood collections (for example, for toxicokinetics or clinical pathology analyses).

While the clinical relevance of antibody development is uncertain, antigenicity was nevertheless a confounding factor in assessing toxicities in the animal studies. Anti rFVIII^{IFc} antibodies were detected in both rat and monkey repeat dose studies with onset of development earliest in high dose group animals. Antibodies were against the FVIII moiety of rFVIII^{IFc} and were found to have a neutralising effect on endogenous FVIII. In monkeys this affected haematological parameters, shown as decreased red blood cells (RBC), haemoglobin and haematocrit levels associated with impairments to haemostasis and haemorrhaging. Antigenicity also caused prolonged aPTT, in which aPTT on days 19 and 27 of treatment was progressively longer in high dose group animals, and persisted (albeit, to a slightly lesser degree) in the recovery cohort animals. With regard to other

toxicological investigations, there were no untoward changes noted in body weight, organ weights, serum chemistry measurements and gross pathology.

Mortalities due to severe haemorrhage occurred at the high dose (1000 IU/kg) in one monkey study, but not in the second monkey study at the same doses. Reasons for the difference between the two studies are not clear, but might be related to the test formulation. A frozen liquid formulation was used in the study with mortalities, while a lyophilised formulation was used in the second study. However, in both studies similar antibody titre levels were noted over a similar onset period. Changes to haematological parameters were also similar, and signs of haemorrhaging and prolonged aPTT were apparent in both investigations. The lyophilised formulation is to be marketed for clinical use and was used in a Phase III clinical trial.

Antibody development against rFVIII_{FC} was also studied in mice. Both rFVIII_{FC} and recombinant coagulation factor VIII (rFVIII) (ReFacto) showed comparable incidence and extent of immunogenicity, particularly at higher doses (250 and 1000 IU/kg) suggesting that the Fc subunit does not confer any greater immunogenicity to rFVIII_{FC} than would be anticipated. Indeed, characterisation of the antibodies showed that they were predominantly against the FVIII moiety rather than the Fc subunit. A second mouse study compared two different lyophilised drug product batches; however, neither batch induced an antigenic response, bearing in mind that a dose of only 50 IU/kg was used compared to 50, 250 and 1000 IU/kg tested in the other mouse study.

Overall, the repeat dose toxicity studies highlighted adverse effects that were secondary to antigenic reactions against rFVIII_{FC} in the test animals. The development of neutralising antibodies against rFVIII_{FC} led to impairments to haemostasis, discolouration of limbs and extremities and aberrant haematological parameters.

Genotoxicity and carcinogenicity

No genotoxicity studies were conducted using rFVIII_{FC}, which is acceptable according to guideline recommendations (ICH S6[R1]) for a recombinant human protein substance not containing an organic chemical linker. The sponsor provided two genotoxicity studies (bacterial reverse mutation and an in vitro chromosomal aberration) on an unrelated substance (alefacept) that contains the same Fc linker, which were previously evaluated by the TGA. Both studies gave negative results.

The absence of carcinogenicity studies is also acceptable on the grounds that standard studies of carcinogenicity in animals are not feasible due to the development of antibodies with repeat administration of biological substances.

Reproductive toxicity

The sponsor did not conduct any reproductive toxicity studies on rFVIII_{FC}. This is acceptable in view of the fact that rFVIII_{FC} is for the replacement of normal, physiological FVIII activity in haemophilia A which is a sex linked disease that occurs predominantly in males. Females are rarely affected therefore exposure to rFVIII_{FC} during pregnancy and embryofetal development is considered remote. Animal studies on fertility, reproductive and developmental toxicity have not been conducted on other registered recombinant clotting factor products (for example Advate and Kogenate). rFVIII has been used in haemophilia A patients for years, and there is no evidence of adverse effects on fertility or embryofetal development.

Pregnancy classification

The sponsor did not nominate a pregnancy category for rFVIII_{FC}. Whilst the patient population affected by haemophilia A and intended to use rFVIII is males with a sex linked disease, there are some rare instances where females are afflicted and thus an appropriate

category should be assigned to convey to prescribers potential risks on fetal health arising from maternal exposure.. Recombinant FVIII and most other coagulant factors are classified as category B2⁷ drugs based on the lack of animal reproductive toxicity studies. Pregnancy category B2 is considered appropriate for rFVIII Fc⁸.

Local tolerance

Assessment of local tolerance to rFVIII Fc was incorporated into the schedule of macroscopic and microscopic observations of the 4 week repeat dose toxicity studies in rats and monkeys. Injection site reactions (perivascular fibrosis, swelling and discolouration of hindlimbs/forelimbs) were noted in medium dose females and high dose males and females from one of the four week monkey studies.. In the second four week monkey study, treatment related changes associated with local reactions were confined to discolouration of extremities where blood collection or dose administration was performed. The findings were secondary to FVIII neutralising antibodies. No other signs of irritation or inflammation (for example oedema, lymphocyte infiltration) were reported in any of the studies.

Paediatric use

rFVIII Fc is indicated for use in adults and adolescents (≥ 12 years old). No juvenile toxicity studies were conducted.

Nonclinical summary and conclusions

- The nonclinical dossier was satisfactory for a biotechnology derived therapeutic product. The clinical route (IV administration) was used in all animal studies, and the animal models used were responsive to the tested article.
- Primary pharmacology studies demonstrated comparable characteristics of rFVIII Fc to registered recombinant FVIII replacement products. Association of rFVIII Fc with the neonatal Fc receptor was demonstrated in a number of species; as well, rFVIII Fc was shown to ably form the tenase complex with activated Factor IX to bring about coagulation. rFVIII Fc was inactivated by APC to a similar extent as a rFVIII comparator product. In animal models of haemophilia A (Hem A mice and Hem A dogs), sustained clotting activity (as both acute and prophylactic protection) was demonstrated and correlated with sustained plasma FVIII levels.
- Safety pharmacology assessments were incorporated in the GLP repeat dose toxicity studies. There were no overt adverse findings to indicate specific effects on the function of critical organ systems.
- The elimination $t_{1/2}$ and plasma FVIII levels were higher for rFVIII Fc than for comparator rFVIII products in all tested species except monkeys. Studies in FcRn KO mice and hFcRn transgenic mice confirmed that prolonged elimination $t_{1/2}$ of rFVIII Fc is dependent on its interaction with the FcRn receptor. Repeat dosing resulted in shorter $t_{1/2}$ and lower AUCs in monkeys, or became undetectable in rats by the last sampling

⁷ 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.*

⁸ The Delegate subsequently assigned efmoctocog alfa(rhu) to use in pregnancy Category C (*Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Accompanying texts should be consulted for further details*) on the basis that placental transfer is a significant consideration and the effects on the developing fetus are unknown.

time because of antibody development. A tissue distribution study in Hem A mice and FVIII/vWF double KO mice showed high uptake of rFVIII in liver and vWF appeared to reduce liver uptake and clearance of rFVIII Fc.

- In a single dose toxicity study in monkeys doses of up to 20,000 IU/kg IV were well tolerated, causing no mortalities or notable acute toxicities.
- Repeat dosing of rFVIII Fc was generally well tolerated by both rats and monkeys with no specific targeted toxicities seen in either species. The development of neutralising anti rFVIII antibodies accounted for most of the adverse findings (impaired haemostasis, subcutaneous haemorrhaging and associated decreases in RBC, haemoglobin and haematocrit).
- Genotoxicity and carcinogenicity studies were not conducted, which is acceptable and consistent with ICH guidelines for biotechnology derived therapeutic products. No reproductive toxicity studies were conducted with rFVIII Fc. Given that haemophilia A is a sex linked disease that occurs in males, rFVIII Fc is a recombinant human protein and no test article related findings were noted in the reproductive organs in the repeat dose toxicity studies, the absence of reproductive toxicity studies is not considered a deficiency of the nonclinical data.
- Repeat dose toxicity studies showed no significant local reactions except for FVIII neutralising antibody related haemorrhage at the injection and blood sampling sites.
- Although the animal models used to assess potential repeat dose toxicities of rFVIII Fc were not ideal due to the development of anti FVIII antibodies, in view of the class of product (replacement human clotting factor) short term administration of rFVIII Fc was well tolerated.
- There are no nonclinical objections to registration.

Recommended revisions to nonclinical statements in the draft PI are beyond the scope of the AusPAR.

IV. 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

Eloctate is a long acting antihemophilic factor (recombinant) indicated in adults and children (≥ 12 years) with haemophilia A (congenital factor VIII deficiency) for control of bleeding episodes, routine prophylaxis to prevent or reduce the frequency of bleeding episodes, and perioperative management (surgical prophylaxis).

Clinical rationale

Haemophilia is an inherited, X linked bleeding disorder. In Australia there are approximately 2,600 people with haemophilia and nearly all are male. Haemophilia A is the most common form and is due to the deficiency of factor VIII. Reduced blood coagulation results in bleeding which is most commonly internal, usually into the joints or muscles. Over time, recurrent bleeds can cause permanent damage such as arthritis, chronic pain and joint damage requiring surgery. Plasma derived coagulation factor concentrates were effective but were associated with a high rate of blood borne viruses such as hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV). Effective rFVIII products have been developed subsequently although their

use is limited by the development of inhibitor (anti rFVIII binding antibody) in up to 30% of patients. Inhibitors develop most commonly within 100 exposure days in previously untreated patients (PUPs) but may also develop in previously treated patients (PTPs). The next generation of recombinant products will be long acting with the aim of reducing the frequency of the IV injections required for long term prophylaxis in patients with severe disease.

Eloctate is a replacement therapy to increase plasma factor VIII levels as a temporary correction of the bleeding tendency in haemophilia A. The FVIII portion of Eloctate is a glycoprotein [functionally] similar to endogenous FVIII found in human plasma. When injected, it binds to von Willebrand factor in the circulation and acts as a replacement for the FVIII deficiency. The other portion of Eloctate is the Fc fragment of human IgG1 which binds to the neonatal Fc receptor which is expressed throughout adult life. This receptor protects immunoglobulins from lysosomal degradation and acts to prolong their plasma $t_{1/2}$. The design of Eloctate enables replacement of all the functions of FVIII with an extended half-life compared with the naturally occurring factor.

Guidance

A pre submission meeting with the TGA was held. The sponsors were requested to justify the use of a single pivotal study, and to justify the lack of randomisation in the clinical trial program in the proposed submission. However, the TGA provisionally accepted the sponsors' justification for the lack of an active comparator control in the pivotal study. Such a non inferiority study would not be feasible because of the large patient numbers required in the orphan haemophilia population.

The TGA has adopted the EMA guideline on rFVIII products (1999⁹) but the latest guideline (2009¹⁰) had not yet been adopted at the time the clinical evaluation was prepared. The TGA has encouraged the sponsor to comply with the earlier guideline but has sought the opinion of the clinical evaluator before considering potential discrepancies further.

Contents of the clinical dossier

The submission contained the following clinical information:

- One Phase I/IIa clinical pharmacology study (998HA101), a completed PK study in PTPs.
- One population PK analysis (CPP-12-026-BIIB031, derived from clinical studies 998HA101 and 997HA301.
- One pivotal Phase III efficacy/safety study A-LONG (997HA301), an open label, uncontrolled, 3 arm study in adult PTPs.
- One interim progress report of the supportive efficacy/safety study (8HA01EXT), an ongoing study in adult PTPs who have completed 997HA301, and paediatric patients who have completed 8HA02PED.
- Clinical Overview, Summary of Clinical Efficacy, Summary of Clinical Safety, Summary of Clinical Pharmacology, Summary of Biopharmaceutic studies and Analytical Methods and literature references.

⁹ CPMP/BPWG/1561/99. Note for guidance on the clinical investigation of recombinant factor VIII and IX products.

¹⁰ EMA/CHMP/BPWP/144533/2009. Guideline on the clinical investigation of recombinant and human plasma-derived factor VII products. [this has since been adopted by the TGA].

Paediatric data

The submission included one progress report from an ongoing efficacy/safety study (8HA02PED), in paediatric PTPs < 12 years with completed patients continuing into 8HA01EXT.

Data from this and the Phase III pivotal study that included previously treated patients aged 12 years and over, will form the basis of a future submission for use in children < 12 years of age.

Good clinical practice

All studies were conducted in compliance with the principles of the ICH guidelines on Good Clinical Practice (GCP) and the ethical principles outlined in the Declaration of Helsinki.

Pharmacokinetics**Studies providing pharmacokinetic data**

PK Studies 998HA101 and the population pharmacokinetic report (CPP12-026-BIIB031) were provided in the dossier. None of the PK studies had deficiencies that excluded their results from consideration.

Evaluator's summary and conclusions on pharmacokinetics

The activity time profiles of rFVIIIFc have been evaluated and compared with rFVIII (Advate) in a Phase I/IIa PK study in 16 patients with haemophilia A. The study used FVIII activity as a surrogate endpoint as recommended by the EMA and the International Society on Thrombosis and Haemostasis (ISTH) to estimate AUC, $t_{1/2}$, mean residence time (MRT) and clearance. rFVIIIFc had a superior PK profile compared with Advate with approximate increases in half-life and MRT of 53% for the 25 IU/kg dose and 76% for the 65 IU/kg dose. The prolongation of activity was due to a 36% reduction in the clearance of rFVIIIFc compared to Advate. The primary PK profile was based on the one stage clotting assay and confirmed by similar results using the chromogenic assay. The compartmental and non compartmental analyses were complemented by the population PK analysis which confirmed the long term stability of the PK parameters. The population PK models adequately described the activity data in the PK and Phase III studies. The major covariate for rFVIIIFc activity was clearance and there was no clinically meaningful influence related to body weight, haematocrit or age.

The PK and the pivotal studies were well conducted and complied with TGA and EMA guidelines. The population PK models derived from the combined data have been used to develop useful dosing recommendations for clinicians.

Pharmacodynamics**Studies providing pharmacodynamic data**

None submitted.

Dosage selection for the pivotal study

Doses of 25 IU/kg and 65 IU/kg were well tolerated in the Phase I/IIa Study 998HA101. Based on the PK data it was estimated that 88% of patients would sustain FVIII trough levels > 1%, 3 days after a 25 IU/kg dose and that 83% of patients would sustain trough levels > 1%, 4 days after a 50 IU/kg dose. Based on these assumptions, the starting dose for Arm 1 of the pivotal study was a twice weekly regimen with 25 IU/kg on the first day followed by 50 IU/kg on the fourth day. Data from 998HA101 were also used to generate dose adjustment algorithms for individualised prophylaxis regimens.

Efficacy

Studies providing efficacy data

Only one efficacy study has been performed.

Pivotal efficacy study

Study 997HA301 (A-LONG) was an open label, multicentre evaluation of the safety, efficacy and PK of rFVIII Fc in the prevention and treatment of bleeding in PTPs with severe haemophilia A. The primary objectives of the study were to compare the efficacy and safety of rFVIII Fc given in various treatment regimens as prophylaxis and on demand during surgical treatment.

Evaluator's conclusions on efficacy

For the assessment of clinical efficacy for control of bleeding episodes, routine prophylaxis to prevent or reduce the frequency of bleeding episodes, and perioperative management (surgical prophylaxis), because of the limited availability of haemophilia A patients, the latest EU Guideline¹¹ (not adopted by the TGA at the time the clinical evaluation was prepared) recommends the enrolment of at least 100 patients, using FVIII activity as a surrogate endpoint and without the need for a control group. The initial study should be conducted in PTPs aged ≥ 12 years with a study in PUPs conducted post marketing. In the pivotal study, a total of 165 patients aged > 12 years were randomised and all were PTPs. Patient numbers were adequate and 13 adolescent patients were included.

Despite the lack of a control group, the study clearly demonstrated that rFVIII Fc is effective in adults and adolescents with haemophilia A. In the pivotal Phase III study, there were 757 bleeding episodes (in 106 patients) of which 97.8% were controlled with ≤ 2 rFVIII Fc injections (87.3% with one injection) with a total median dose per injection of 28 IU/kg. A total of 78.1% of patients evaluated the response to the first injection as excellent or good. The investigators' global assessment of response was rated as excellent or effective for 99.3% of the patient visits. Prophylactic treatment was more effective than episodic treatment. In Arm 1 of the pivotal study (prophylaxis tailored to FVIII trough levels), 45.3% of patients had no bleeding episodes during the efficacy period with a 92% reduction ($p < 0.001$) in annualised bleeding rate compared with Arm 3 (the episodic treatment group). Single dose weekly prophylaxis was less effective than tailored prophylaxis but 14.5% of patients in Arm 2 had no bleeding episodes during the study. Nine major surgeries were performed in nine patients during the study. The response to rFVIII Fc was excellent in eight cases and good in one case after a single preoperative dose to maintain haemostasis (median dose 51.4 IU/kg).

¹¹ EMA/CHMP/BPWP/144533/2009. Guideline on the clinical investigation of recombinant and human plasma-derived factor VII products.

The study conduct was satisfactory and the efficacy results support the use of rFVIII Fc for control of bleeding episodes, routine prophylaxis and perioperative management.

Safety

Studies providing evaluable safety data

Study 997HA301 provided evaluable safety data. There were few adverse events (AEs) in the PK study 998HA101 with no serious adverse events (SAEs) or deaths. The study contributed less than 0.2% of the total rFVIII Fc exposure and these safety data are not assessed further.

Pivotal efficacy studies

In the pivotal efficacy study, the following safety data were collected:

- AEs, SAEs and deaths.
- AEs of special interest, including inhibitor development, anaphylaxis, hypersensitivity events, serious thrombotic events, or suspected infectious agent transmission were reported to the Sponsor as SAEs irrespective of whether they met the criteria for SAEs.
- Laboratory tests were performed at a central laboratory.

Other studies evaluable for safety only

Study 8HA02PED

Study 8HA02PED is an open label, multicentre evaluation of the efficacy, safety and PK of rFVIII Fc for routine prophylaxis in paediatric PTPs with haemophilia A. The first patient was enrolled in August 2012 and the study is still ongoing. The cut-off point for this interim analysis was January 2013. The data have been used for evaluation of SAEs and AEs of special interest and no efficacy data have been analysed.

The primary objective of the study is to evaluate the safety of rFVIII Fc in paediatric PTPs with haemophilia A. The primary endpoint of the study is the frequency of inhibitor development.

At the cut-off point, 33 patients have been enrolled into the study and 23 have received at least one dose of rFVIII Fc. Patient demographics were provided. Of the 33 patients, 33% were < 6 years old and the remainder were aged in the range 6 to 12 years. The majority of patients were White (58%) and 21% were Black.

To date, no deaths have been reported. One treatment emergent SAE has been reported: a device-related infection considered unrelated to treatment.

Study 8HA01EXT

This is an extension study to the Phase III study 997HA301 and the paediatric study 8HA02PED. It is an open label, multicentre evaluation of the long term safety and efficacy of rFVIII Fc for prophylaxis and episodic (on demand) treatment of bleeding episodes in PTPs with haemophilia A. The study is still ongoing. The primary objective of the study is to evaluate the long-term safety of rFVIII Fc. The secondary objective is to evaluate the efficacy of rFVIII Fc in the prevention and treatment of bleeding episodes.

As of 7 January 2013, 150 patients from 997HA301 were enrolled and received at least one dose of rFVIII Fc, 95 of whom completed the first 6 month safety visit.

No AE data have been analysed at the January 2013 cut off. There were no deaths. There were 10 SAEs reported by 8 patients all of which were considered unrelated to study treatment. There were no AEs of special interest (inhibitors, anaphylaxis, serious

hypersensitivity or thrombotic events). No unique safety features were identified in the adolescent group.

Patient exposure

Patient exposure data are limited to the pivotal Phase III Study 997HA301. The extension Studies 8HA01EXT and 8HA02PED are still ongoing and the PKStudy CPP-12-026-BIIB031 contributed less than 0.2% of the overall exposure data. Exposure in the pivotal study is shown in Table 2 and Table 3. A total of 164 patients received at least one dose of rFVIIIFc for a median duration of 30.5 weeks (range < 1 to 54 weeks). Overall, 97.0%, 89.0%, 14.0% and 3.7% of patients received treatment for at least 13, 26, 39 and 52 weeks, respectively. For all dosed patients the median total exposure days (EDs) was 57 (range 1 to 123), with 111 patients having ≥ 50 EDs. The mean total number of injections given was 57 (range 1 to 136).

Table 2: Study 997HA301. Duration of dosing with rFVIIIFc safety analysis set.

	Arm 1 (N=118)	Arm 2 (N=24)	Arm 3 (N=23)	Total (N=165)
Cumulative number of weeks on rFVIIIFc (a)				
At least 13 weeks	116 (99.1%)	20 (83.3%)	23 (100.0%)	159 (97.0%)
At least 26 weeks	122 (95.7%)	16 (66.7%)	19 (78.3%)	144 (89.0%)
At least 39 weeks	23 (19.7%)	0	0	23 (14.0%)
At least 52 weeks	6 (5.1%)	0	0	6 (3.7%)
Total weeks on rFVIIIFc				
n	137	24	23	164
Mean (SD)	34.2 (8.15)	24.4 (9.78)	28.1 (8.80)	31.9 (8.78)
Median	30.1	28.0	28.9	30.5
Min, Max	5, 54	<1, 39	15, 32	<1, 54

NOTE 1: Percentages are based on the number of subjects who received rFVIIIFc in each treatment arm or overall. Subject 581-002 (Arm 1) received only Advate.
 2: Time on rFVIIIFc refers to the length of time from the first rFVIIIFc PK dose through the last day of the efficacy period.
 (a) A subject can appear in more than one category.

Table 3: Study 997HA301. Exposure data. Summary of injections and days of exposure to rFVIIIFc. Safety analysis set.

	Arm 1 (N=118)	Arm 2 (N=24)	Arm 3 (N=23)	Surgery subgroup (N=9)	Total (N=165)
Total exposure days (a)					
<50	9 (7.7%)	23 (95.8%)	21 (91.3%)	1 (11.1%)	53 (32.3%)
≥ 50	108 (92.3%)	1 (4.2%)	2 (8.7%)	8 (88.9%)	111 (67.7%)
n	117	24	23	9	164
Mean	67.4	30.0	24.4	79.4	55.9
SD	17.84	14.95	14.86	26.21	24.93
Median	64.0	30.5	21.0	79.0	57.0
Min, Max	16, 123	1, 75	7, 63	35, 123	1, 123
Total number of injections per subject					
n	117	24	23	9	164
Mean	68.9	30.2	24.8	91.7	57.0
SD	19.60	14.99	15.16	32.36	26.26
Median	65.0	30.5	22.0	93.0	57.0
Min, Max	16, 136	1, 75	7, 65	37, 136	1, 136

NOTE 1: Percentages are based on the number of subjects in each treatment arm or overall.
 2: Subjects in the surgery subgroup are also counted in the other arm in which they participated. Each subject is counted only once in the total column. Subject 581-002 (Arm 1) received only Advate.
 (a) An exposure day is a 24 hour period in which one or more rFVIIIFc injections are given.
 All injections over the study course are counted.

Safety issues with the potential for major regulatory impact

Liver toxicity

No issues identified.

Haematological toxicity

No issues identified.

Serious skin reactions

No issues identified.

Cardiovascular safety

No issues identified.

Unwanted immunological events

No issues identified.

Evaluator's conclusions on safety

In general, rFVIIIFc was well tolerated. In the single pivotal Phase III study, 164 previously treated adult and adolescent patients with haemophilia A received at least one dose of rFVIIIFc. The study was sufficient in size to adequately assess the risk of inhibitor formation and very common or common AEs. A total of 146 patients have been treated for at least 26 weeks and a long term extension study is ongoing. There was no placebo control group but the types and incidence of AEs were consistent with those expected in the haemophilia population. With the exception of arthralgia recorded in 7.9% of patients, the most common AEs [nasopharyngitis (12.2%), headache (7.9%) and upper respiratory tract infection (URTI) (5.5%)] are commonly reported in the general population. No deaths or SAEs were considered related to rFVIIIFc treatment by Investigators. The pattern of infections was unremarkable and there was no evidence of immune compromise or increased risk of infection. The AE profile in patients with underlying HIV/HCV was similar to the rest of the patient population. Safety in adolescents appeared similar to that of the adults and there appeared to be no effects related to race, BMI or geographic region. There were no meaningful patterns or trends in clinical chemistry, haematology or vital signs. No patient developed an inhibitor or other AEs of special interest. Target organ toxicity is not a feature of biologics but there were no cases of anaphylaxis or hypersensitivity reactions. In keeping with the orphan population, limited patient numbers have been treated but no safety signals have been detected to date.

First round benefit-risk assessment**First round assessment of benefits**

The benefits of Eloctate in the proposed usage are:

- Effective control of bleeding with 87.3% of acute bleeds controlled with a single injection.
- Effective as routine individualised prophylaxis with 92% reduction in annualised bleeding rates compared with episodic (on demand) treatment.
- Effective as once weekly prophylaxis with 76% reduction in annualised bleeding rates compared with episodic (on demand) treatment.
- Effective for perioperative management with 100%, excellent or good haemostasis.
- A long half-life (18.97 h¹²), 1.53 fold longer than Advate (rFVIII).

¹² Based on data from Study 997HA301.

- Reduced dosing frequency. Almost 90% of patients had a history of requiring three or more prophylaxis injections/week of FVIII before the study, compared with an average dosing interval of 3 days or longer on rFVIIIFc.
- Clear dosing recommendations based on population PK data.
- No cases of inhibitor formation in 110 patients with at least 50 EDs (upper bound of 95% confidence interval (CI) was 3.3%).
- Fully recombinant with no human or animal additives.
- Well tolerated with no anaphylaxis or hypersensitivity reactions to date.

First round assessment of risks

The risks of Eloctate in the proposed usage are:

- The safety database includes only 180 patients aged ≥ 12 years. Uncommon AEs such as hypersensitivity reactions may not have been detected.
- Long-term safety has not been established.
- No safety data in children aged < 12 years.
- No safety data in PUPs (at higher risk of inhibitor development).
- Risk of severe hypersensitivity reactions not yet known.

First round assessment of benefit risk balance

The benefit risk balance of Eloctate, given the proposed usage, is favourable.

First round recommendation regarding authorisation

Authorisation is recommended for the use of Eloctate in adults and children (≥ 12 years) with haemophilia A for control and prevention of bleeding episodes; routine prophylaxis to prevent or reduce the frequency of bleeding episodes; and perioperative management (surgical prophylaxis). Approval is subject to satisfactory response to questions raised.

The TGA Delegate has expressed concern about whether the data support an indication that encompasses adult and/or adolescent patients. The EMA Guidelines on recombinant coagulation factor VIII (rFVIII) products (2000 and 2009 versions) are silent on adolescents and recommend patient studies in an inclusive population aged ≥ 12 years. Although there is no specific requirement, the safety and efficacy study included 13 adolescent patients whose response was similar to that of the adult population.

Clinical questions

Pharmacokinetics

Would the sponsors suggest why all the reported bleeding events in the PK study 998HA101 occurred in the rFVIIIFc group and none in the Advate group?

Efficacy

In the pivotal study, 26.8% of patients had major informed consent 'issues'. Please clarify and provide assurance that the study was performed to full GCP and was adequately monitored.

Second round evaluation of clinical data submitted in response to questions

The sponsor responses to clinical questions (above) were taken into account in the Delegate's overview. See *Overall conclusion and risk/benefit assessment*.

With regard to the question on pharmacokinetics the Delegate noted that the disparity in reported bleeding between Advate and rFVIIIFc groups was due to the study design and the limited follow up period for Advate (4 days).

With regard to the question on efficacy the issue was resolved to the satisfaction of the Delegate.

Therefore a second round evaluation report was not prepared.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted Australian risk management plan (RMP) version 1, data lock point 14 September 2012 which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 4.

Table 4: Summary of ongoing safety concerns.

Ongoing safety concerns	
Important identified risks	None
Important potential risks	<p>Inhibitor development</p> <p>An inhibitor is defined as a neutralising antibody value ≥ 0.6 Bethesda units [BU]/mL, identified and confirmed by retesting of a second sample within 2 to 4 weeks.</p> <p>Allergic reaction or anaphylaxis</p> <p>A serious allergic reaction associated with administration of rFVIIIFc is defined as an event that is \geq Grade 2 on the Recommendations for Grading of Acute and Subacute Toxic Effects on the World Health Organisation scale.</p>
Important missing information	<p>Safety profile in patients ≥ 65 years old</p> <p>Safety profile in children < 12 years old</p>

Pharmacovigilance plan

Routine pharmacovigilance activities are proposed to address all ongoing safety concerns. Additional pharmacovigilance activities are proposed to address the two potential risks of inhibitor development and anaphylactic/hypersensitivity.

The additional activities described by the sponsor are: 1.) *Expedited reporting to regulators of inhibitors* and 2.) *Targeted follow-up by questionnaire of inhibitors from spontaneous*

reports, other programs where data are being handled as solicited, and all clinical trial serious adverse events (SAEs).

Moreover, to address the two potential risks of “Inhibitor development” and “Hypersensitivity/Anaphylactic reaction” and the missing information of “Safety profile in children < 12 years old” two clinical trials are ongoing at the time of evaluation.

Risk minimisation activities

With regard to the need for risk minimisation activities, the sponsor has concluded: *“Prophylactic treatment with long-acting rFVIII Fc was associated with improvement in quality of life in subjects switching from prior episodic dosing. In clinical development, rFVIII Fc was well tolerated and no new or unexpected safety issues were identified in any subpopulations. The incidence of inhibitor formation in PTPs was 0% (95% CI 0%, 3.3%), which is in the acceptable range for a new therapy for haemophilia A. There were no cases of anaphylaxis, serious vascular thrombosis (except a probable haemorrhoid), or suspected transmission of an infectious agent. The overall benefit-risk profile of rFVIII Fc is positive for the treatment of individuals with haemophilia A. Because the most important risks of rFVIII Fc treatment remain potential risks rather than known risks, it is proposed that the potential risks can be appropriately managed and minimised by guidance in the Product Information without requirement for any enhanced risk minimisation.”*

Routine risk minimisation activities are proposed to address all ongoing safety concerns.

Reconciliation of issues outlined in the RMP report

Table 5 summarises the OPR’s first round evaluation of the RMP, the sponsor’s responses to issues raised by the OPR and the OPR’s evaluation of the sponsor’s responses.

Table 5: Reconciliation of issues outlined in the RMP report.

Recommendation in RMP evaluation report	Extract of the Sponsor’s s31 RMP response	OPR evaluator’s comment
<p>It is brought to the Delegate’s attention that the proposed indication in Australia includes “Perioperative management (surgical prophylaxis)”, although it appears that this was not the indication granted orphan drug status.</p>	<p>Biogen Idec’s application for orphan drug designation, specified the following indications which are consistent with the indications presented in the proposed labelling:</p> <ul style="list-style-type: none"> • Control and prevention (including routine prophylaxis) of bleeding episodes in adults and children with Haemophilia A; • Perioperative management in adults and children with Haemophilia A. <p>However, the letter from the TGA, informing Biogen Idec that rFVIII Fc was designated as an orphan drug, noted that</p>	<p>The response is noted. However, this issue is drawn to the attention of the Delegate for consideration.</p>

Recommendation in RMP evaluation report	Extract of the Sponsor's s31 RMP response	OPR evaluator's comment
	<p>“the indication is for the control and prevention (including routine prophylaxis) of bleeding episodes in adults and children with haemophilia A.”</p> <p>Biogen Idec's interpretation of the TGA's orphan designation letter was that the use of rFVIII Fc for perioperative management (surgical prophylaxis) was covered under the broader indication for “the control and prevention (including routine prophylaxis) of bleeding episodes.”</p>	
<p>It is recommended that the sponsor provides follow up forms to collect information regarding adverse events for the two potential risks of “Inhibitor development” and “Allergic reactions or anaphylaxis” for review prior to approval.</p>	<p>Should the Delegate request follow-up forms for the potential risks of “Inhibitor development” and “Allergic reactions or anaphylaxis” as recommended by the evaluator, Biogen Idec agrees to provide them for review prior to approval.</p>	<p>This response is considered unacceptable.</p> <p>The RMP is not the Delegate's responsibility but that of the RMP evaluator and the director of the RMP section. Furthermore, the sponsor has specified the use of follow up forms for the two potential risks of Inhibitor development and Anaphylactic/Hypersensitivity in the RMP provided for evaluation. Submission of these documents is a basic requirement for submission of a valid RMP. In the TGA guideline “Risk Management Plan (RMP) Questions & Answers, Version 1.3, October 2012”¹ “it is stated:</p> <p><i>“What must be included</i></p>

Recommendation in RMP evaluation report	Extract of the Sponsor's s31 RMP response	OPR evaluator's comment
		<p><i>in the RMP? Particular attention should be paid to ensuring: - all attachments, annexes and appendices referred to in the RMP are included in full. This excludes the Eudravigilance Annex 1."</i></p> <p>Consequently, the RMP in its current version is incomplete and therefore considered unacceptable.</p>
<p>It is recommended that the sponsor provides an RMP in the EU format, including the section "Additional EU requirements" including the points: 1.) Potential for overdose, 2.) Potential for transmission of infectious disease, 3.) Potential for misuse for illegal purposes, 4.) Potential for off label use and 5.) Potential for paediatric off-label use, and other required information specified in the TGA guideline RMP Q&As document version 1.3, dated Dec-2012*.</p>	<p>Biogen Idec aims to provide the TGA a RMP in the EU format, including the section "Additional EU requirements" including the points: 1.) Potential for overdose, 2.) Potential for transmission of infectious disease, 3.) Potential for misuse for illegal purposes, 4.) Potential for off label use and 5.) Potential for paediatric off-label use, and other required information specified in the TGA guideline*.</p>	<p>This response is considered insufficient. The sponsor has not provided the RMP in the requested format, and did not specify a date for submission of the requested document. It is recommended that the sponsor submits the requested RMP document for review prior to approval.</p>
<p>The following recommendations are made regarding amendments to the table of ongoing safety concerns:</p> <p>A.) It is recommended that patient groups with hepatic and renal impairment be included as missing information in the table of ongoing safety concerns. Pharmacovigilance and risk minimisation activities should be assigned as appropriate.</p> <p>B.) It is recommended that the sponsor provides detailed comments on the available data indicating that the safety for patient groups with HIV and</p>	<p>Should the Delegate request these RMP amendments as recommended by the evaluator, Biogen Idec agrees to add the following patient groups, including pharmacovigilance and risk minimisation activities for these patients groups as appropriate, as missing information in the table of ongoing safety concerns:</p> <p>A). patient groups with hepatic and renal impairment</p> <p>B). patient groups with HIV</p>	<p>The sponsor's justification for not including the following information at present is acceptable.</p> <ol style="list-style-type: none"> 1. patient groups with HIV and HCV, 2. patients with mild to moderate haemophilia, 3. thrombotic events. <p>The recommendation remains to include the</p>

Recommendation in RMP evaluation report	Extract of the Sponsor's s31 RMP response	OPR evaluator's comment
<p>HCV has been established. If the safety for the product has not been satisfactorily established for these patient groups, then it is recommended that these patient groups be included in the ongoing table of safety concerns, and pharmacovigilance and risk minimisation activities should be assigned as appropriate.</p> <p>C.) It is recommended that "previously untreated patients" be included in the table of ongoing safety as missing information. Pharmacovigilance and risk minimisation activities should be assigned as appropriate.</p> <p>D.) It is recommended that "patients with mild to moderate haemophilia" be included in the table of ongoing safety as missing information. Pharmacovigilance and risk minimisation activities should be assigned as appropriate.</p> <p>E.) It is recommended to the Delegate to draw the attention of the clinical evaluator to assess whether it is appropriate not to include thrombotic events in the table of ongoing safety concerns.</p>	<p>and HCV</p> <p>C). previously untreated patients</p> <p>Biogen Idec does not think it would be informative to add the following items to the table of ongoing safety concerns as missing information in the table of ongoing safety concerns based on the clinical evidence summarised below:</p> <p>D). patients with mild to moderate haemophilia</p> <p>E). thrombotic events</p>	<p>following in the table of ongoing safety concerns as missing information: A.) patient groups with hepatic and renal impairment and C.) previously untreated patients.</p> <p>Risk-Minimisation and pharmacovigilance activities should be assigned as appropriate.</p>
<p>It is recommended that the RMP be revised to include adherence of the pharmacovigilance activities in accordance to the Australian requirements as described in the document "Australian requirements and recommendations for pharmacovigilance responsibilities of sponsors of medicines", version 1.1, dated Dec-2012.</p>	<p>Should the Delegate request the RMP be revised as recommended by the evaluator, Biogen Idec will revise the RMP to include adherence of pharmacovigilance activities in accordance to the Australian requirements.</p>	<p>The RMP is not the Delegate's responsibility but that of the RMP evaluator and the director of the RMP section.</p> <p>This recommendation remains.</p>
<p>It is recommended that the sponsor revises the RMP to include submission dates for</p>	<p>Should the Delegate request revisions to the RMP to include submission dates for</p>	<p>The RMP is not the Delegate's responsibility but that</p>

Recommendation in RMP evaluation report	Extract of the Sponsor's s31 RMP response	OPR evaluator's comment
interim and final study data to the TGA.	data from ongoing studies to the TGA as recommended by the evaluator, Biogen Idec agrees to modify the tables of the RMP to indicate [the requested information]	of the RMP evaluator and the director of the RMP section. This recommendation remains.
It is recommended that the sponsor amends the RMP to list the use of follow up forms as routine risk minimisation activity.	Should the Delegate request the RMP be amended as recommended by the evaluator, Biogen Idec will amend the RMP to list the use of follow up forms as routine risk minimisation activity.	This response is considered unacceptable. The RMP is not the Delegate's responsibility but that of the RMP evaluator and the director of the RMP section. Furthermore, in accordance with the relevant EU guideline, the use of specific questionnaires as a follow-up to a reported suspected adverse reaction is considered to be routine pharmacovigilance. Consequently the RMP should be amended accordingly. The RMP in its current version is unacceptable.
The RMP is lacking discussion/provision of information about certain clinical aspects highly relevant to the use of the product in the targeted patient population. This includes the increased risk of antibody development for patients with high risk gene mutations (Gouw et al. ¹³ , Gosh et al. ¹⁴). It is recommended that the sponsor revised the RMP to include discussion on this point, and describes how it has been	The eligibility criteria for the Phase III study were selected to ensure a representative study population of PTPs with severe haemophilia A. No inclusion or exclusion criteria in the Phase III study restricted the study population based upon gene mutations. In addition, genotype data were collected from study participants and was representative of the expected mutation	This response is considered insufficient. The sponsor states: A revised RMP will include a discussion on the effect of the exclusion criteria across the clinical trial program and the implications for treatment of the target population. However, the sponsor has not submitted the updated

¹³ Gouw S et al. The Multifactorial Etiology of Inhibitor Development in Hemophilia: Genetics and Environment. *Seminars Thrombosis and Hemostasis* 2009;35:723-734.

¹⁴ Gosh S et al. Immune Response to FVIII in Hemophilia A: An Overview of Risk Factors. *Clinic Rev Allerg Immunol.* 2009 37:58-66.

Recommendation in RMP evaluation report	Extract of the Sponsor's s31 RMP response	OPR evaluator's comment
considered in the clinical development program and in the generation of the RMP.	frequencies in the general population of patients with haemophilia A. A revised RMP will include a discussion on the effect of the exclusion criteria across the clinical trial program and the implications for treatment of the target population.	RMP, and it is unclear when the sponsor is going to submit the updated RMP. This recommendation remains.
The consumer medicine information (CMI) and directions for use (DFU) are considered part of the risk management, and therefore, it is recommended that section "Sponsor's conclusion in regard to the need for risk minimisation activities" of the RMP be revised to make reference to the CMI and DFU.	Biogen Idec believes that the risk management described in the CMI and DFU is based upon information provided in the Product Information (PI). Therefore, Biogen Idec believes that the CMI and DFU documents do not warrant a separate reference within the RMP.	This response is considered unacceptable. In accordance with the relevant EU guideline, the package leaflet (equal to the Australian CMI) is considered a separate routine risk-minimisation activity. Consequently, it is expected that the CMI/DFU are referenced in the RMP. This recommendation remains.
It is recommended that an "offlabel use" section be included in a revised RMP. This should include, but not be limited to, off label use for Immuno Tolerance Induction Therapy (ITI) (Rivard et al. ¹⁵). The revised RMP should include a discussion on how this point has been considered during the clinical development program and in the generation of the RMP. Pharmacovigilance and risk minimisation activities should be assigned as appropriate.	Biogen Idec will revise the RMP to include a section on post authorisation off label use including, but not limited to, off label use for (ITI). The document will also include a discussion of how "off label use" was considered during the clinical development program and in the generation of the RMP.	This response is considered insufficient. The sponsor has not submitted the updated RMP, and it is unclear when the sponsor is going to submit the updated RMP. This recommendation remains.
It is recommended that the sponsor amends the RMP to include a discussion about the	Biogen Idec acknowledges that appropriate materials and training will be required	The sponsor describes the use of: 1.) Infusion training kits and 2.) a

¹⁵ Rivard GE et al., Immune tolerance induction in haemophilia A patients with inhibitors by treatment with recombinant factor VIII: a retrospective non-interventional study, *Haemophilia* (2013), 19, 449-455.

Recommendation in RMP evaluation report	Extract of the Sponsor's s31 RMP response	OPR evaluator's comment
<p>use of the product in a home treatment setting, and provides information on how any risks associated with this treatment setting will be addressed in the RMP.</p>	<p>in order to facilitate appropriate preparation, administration and storage of the product for those patients and carers who choose to self-administer Eloctate.</p> <p>The PI, CMI and DFU will be included in each Eloctate pack insert. Therefore, each patient will receive a copy of these materials. Biogen Idec believes that the CMI and DFU documents do not warrant a separate reference within the RMP.</p> <p>In addition, infusion training kits are being developed which will be provided free of charge to haemophilia centres and appropriate health care providers.</p> <p>A patient pack consisting of educational materials will also be provided to all new Eloctate patients.</p> <p>Biogen Idec believes that the potential increased risk of inappropriate preparation, administration and storage of the product has been adequately addressed by the measures detailed above.</p>	<p>patient pack.</p> <p>These activities represent additional risk minimisation activities. Consequently, these activities should be referenced in the RMP, which is currently not the case. Furthermore, a description of the Infusion training kits and patient pack packs has to be submitted for review prior to approval. These documents should be attached as annex to the updated RMP. In addition, the recommendation made in the round 1 RMP report remains.</p>

The remaining OPR recommendations related to revisions to product labelling and the DFU document. Details of these are beyond the scope of the AusPAR.

Advisor committee considerations

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

The application was submitted for advice from the ACSOM.

Outstanding issues

Issues in relation to the RMP

The sponsor has insufficiently or unacceptably addressed the majority of the recommendations made in the round 1 RMP report. The majority of the recommendations made in the round 1 RMP report remain (see Table 5 above).

Recommendation

- The Australian Risk Management Plan version 1, data lock point 14-Sep-2012 to be revised to the satisfaction of the TGA, must be implemented.
- Recommendations made in the section “outstanding issues” must be addressed to the satisfaction of the OPR prior to approval.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate’s overview and recommendations:

Background

Australian clinical guidelines for treatment of Haemophilia A include: *Evidence-based clinical practice guidelines for the use of recombinant and plasma-derived FVIII and FIX products (NBA / AHCDO, 2006)*. Therapy rests on replacement. Currently registered recombinant products include:

Kogenate FS (octocog alfa), Advate (octocog alfa), Xyntha (moroctocog alfa), and NovoEight (turoctocog alfa).

Baxter also has an earlier generation product, Recombinate, on the ARTG. Registered plasma-derived FVIII products include Octanate and (with vWF) Biostate and Wilate.

FVIII in recombinant products has a half-life of approximately 10 to 15 hours (compared with Eloctate: approximately 17.7 hours¹⁶), resulting in similar dosing frequencies across registered products (in adults). The general approach is to modify dosage regimens (dosage intervals, doses) based on individual factors: bleeding phenotype but also individual PK.

Quality

There were no Module 3 objections to registration.

Evaluated data support a shelf-life of 1 year at -70°C for drug substance and 1 year at 2 to 8°C for drug product. There were insufficient data to support storage of the product for up to 6 months at room temperature. Recommendations were made to modify statements regarding storage conditions that are found on labels and in the PI.

The following comment was made about specifications:

“The evaluator has concern with regarding the high specification limit set for non processed isoform (SCrFVIII Fc). The clinical experience to date has only been with product that has less SCrFVIII Fc. Although this form of the product is active and should not impact the in vivo activity of the product the effects of exposure to significant levels of this are not tested.”

The quality evaluator has recommended a conditions of registration regarding limits for aggregates and batch release . Details of these conditions are beyond the scope of the AusPAR.

¹⁶ Data from study 998HA101 for pharmacokinetics based on the one-stage clotting assay for 25 IU/kg rFVIII Fc.

Nonclinical

There were no nonclinical objections to registration. Studies in FcRn KO mice confirmed that the longer elimination half-life of rFVIII Fc is due to interaction with FcRn.

Clinical

The application was supported by the following:

- Pivotal Phase III Study A-LONG (997HA301), an uncontrolled study in adolescent and adult PTPs.
- A population PK analysis (CPP-12-026-BIIB031) derived from clinical studies 998GA301 and 997HA301 data.
- Phase I/IIa Pharmacokinetic Study 998HA101, in PTPs including a subset of patients in 997HA301).
- 8HA02PED, a progress report of use in paediatric PTPs < 12 years.
- 8HA01EXT, an extension study enrolling patients from A-LONG and 8HA02PED.

Information about formulations used across the clinical study programme was provided. The formulation proposed for commercial use differs (in manufacture) from the pivotal Phase III study formulation; a comparability exercise included physicochemical and in vitro characterisation, and PK evaluation in animal models.

Pharmacokinetics

Study 998HA101 was a cross over study comparing rFVIII Fc and Advate, in previously treated adults with severe haemophilia A. Washout was 4 + days (Advate was given first for each patient). Two doses were assessed, in different patients: 25 IU/kg (n = 6, median age 42 years) and 65 IU/kg (n = 10, median age 30 years). Based on the one stage clotting assay, at the 25 IU/kg dose, half-life for rFVIII Fc was 17.7 hours, versus 11.57 hours for Advate (rFVIII Fc 53% higher). At 65 IU/kg, values were 17.24 hours and 9.96 hours respectively (rFVIII Fc 76% higher). Other PK parameters aligned with these differences. There was a disparity in reported bleeding (all 13 reports were after rFVIII Fc) but the study was designed so that there were only 4 days during which a bleed could have occurred 'on Advate'.

Population PK analysis CPP-12-026-BIIB031. This analysis drew on data from 997HA301 A-LONG (n=164) and 998HA101 (n=16). Models were created for Advate and rFVIII Fc. For the prophylaxis model, a key finding was that the 65 IU/kg weekly dose regimen resulted in 27% of subjects remaining above 1% activity at trough, whereas the 50 IU/kg q5day regimen resulted in 53.4% remaining above the 1% threshold. Details of the treatment model are provided in the CER (Attachment 2); one conclusion was that only in isolated cases would > 1 dose be needed within 1 to 2 days for mild moderate bleeds. The target range of 80 to 100 IU/dL for major bleeds was stated as attainable with 24 to 48 hourly infusions. The major covariate for rFVIII Fc activity was clearance.

Efficacy

A-LONG (997HA301)

The study was an open label study of rFVIII Fc in previously treated adults and children ≥ 12 years with severe haemophilia A. In a subgroup there was a single dose cross over PK comparison with Advate (Study 998HA101. – see PK section above); otherwise the study was uncontrolled. There were 3 arms:

- Arm 1: individualised prophylaxis (25-65 IU/kg every 3-5 days to maintain trough 1 - 3% activity); the PK subgroup was drawn from this arm.
- Arm 2: weekly prophylaxis (65 IU/kg every 7 days).
- Arm 3: episodic (on demand) dosing.
- Perioperative management subgroup (patients from Arms 1 - 3 who needed major surgery).

The rationale for dosage selection in this study is provided in the CER.

There was randomisation into Arms 2 or 3, for those subjects previously using an on demand approach who did not want to enter Arm 1 directly; otherwise the study was not randomised.

165 patients were enrolled and 153 completed the study. In Arm 1, there were 118 patients; in Arm 2, there were 24 patients; in Arm 3, there were 23 patients. Informed consent issues were identified in 27% of subjects, but the sponsor clarified that in only 3 out of 44 patients were issues considered significant, and in 3 out of 3 cases the deviations were corrected on study.

All patients were male; the median age was 30 years (range 12-65). There were 13 patients aged 12 to 17 years. The median number of bleeds in the prior 12 months was 6.0 in Arm 1 patients who had been on a prophylactic regimen; across patients who had been on an on-demand regimen, median number of bleeds was 24 to 29.5. Two patients withdrew because of AEs, and 1 patient died (suicide).

Estimated annualised bleeding rate over the efficacy period was 2.9 for Arm 1, 8.9 for Arm 2 and 37.3 for Arm 3. Annualised, no bleeding was estimated for 45.3% of subjects in Arm 1, 17.4% in Arm 2 and 0% in Arm 3. In the 11 adolescents in Arm 1, the median annualised bleeding rate was 1.92 (similar to the rate for patients 18 to 65 years, at 1.44).

Around 78% of patients considered that responses to rFVIIIFc injections for a bleeding episode were good or excellent, across arms. Other efficacy results are described in the CER. Nine major surgeries were performed; haemostasis was excellent or good in all cases.

Safety

The clinical evaluator considered that Phase III Study 997HA301 provided the best characterisation of safety for rFVIIIFc, but noted that safety data were also presented from ongoing Study 8HA02PED. Only 23 patients had received 1 + dose, and only one treatment emergent SAE has been reported (infection, considered unrelated to rFVIIIFc). There were also safety data from those A-LONG patients who rolled over into Study 8HA01EXT. 150 patients had rolled over, 95 of whom had completed the first 6 month safety visit. There were 10 SAEs in 8 patients, all unrelated to treatment and none of special interest (no inhibitors, anaphylaxis, serious hypersensitivity, orthrombotic events).

In 997HA301, 164 patients received 1 + dose of rFVIIIFc for a median duration of 30.5 weeks; 89% of patients received treatment for 26 + weeks but only 3.7% for 52 + weeks. The median number of exposure days was 57 (range 1 to 123), with 111 patients having > 50 EDs.

A description of AEs in 997HA301 is in the CER (see AusPAR Attachment 2). No patients developed an inhibitor (neutralising antibody, ≥ 0.6 BU/mL); there were no SAEs of allergic reaction, anaphylaxis or serious hypersensitivity; there were no SAEs of thrombotic events. One bleeding episode was an SAE; this was a hip haemarthrosis not considered related to treatment (which was presumably captured in efficacy results). There was no sign of a worse safety profile in adolescents.

Clinical evaluator's recommendation

The clinical evaluator recommended approval for the use of Eloctate in adults and children (≥ 12 years) with haemophilia A for control and prevention of bleeding episodes; routine prophylaxis to prevent or reduce the frequency of bleeding episodes; and perioperative management (surgical prophylaxis). Approval is subject to satisfactory response to questions raised.

Risk management plan

The RMP proposed by the sponsor was considered unacceptable by the RMP evaluation section, in some areas. Advice from ACSOM was pending; this may help inform decisions regarding changes to the RMP required before approval. The sponsor proposes to submit an updated RMP in response to this overview to address many issues raised by the RMP evaluator¹⁷. Some specific topics are considered under 'Delegates considerations' below.

Risk-benefit analysis

Delegate's considerations

Efficacy

It is not possible to compare efficacy in Arms 1 and 2 formally, because there was no randomisation into these arms and imbalance in baseline prognostic factors may bias the efficacy outcomes across arms.

A weekly prophylactic regimen might improve patient compliance and adherence to prophylaxis. Notwithstanding the comment above about comparisons across Arms 1 and 2, efficacy appears lower with the weekly option (consistent with the PK results with the 65 IU/kg weekly option).

The Delegate proposed to seek the advice of the Advisory Committee on Prescription Medicines (ACPM) on whether a weekly 65 IU/kg dosing strategy be endorsed, in routine prophylaxis.

Safety

The safety profile of Eloctate is consistent with other rFVIII products, in the population studied. Inhibitor development was not seen but difference in the rate of inhibitor development between Eloctate and other products may be better detected in studies of previously untreated and / or paediatric patients.

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.

Risk management plan

The sponsor proposes to provide an updated RMP in response to the Delegate's overview. It remains to be seen whether this update resolves issues considered critical by the RMP evaluator.

¹⁷ The sponsor subsequently provided an RMP that reflected the TGA requested changes.

RMP – Timing of home treatment

A recommendation has been made by the RMP evaluator regarding the PI text on timing of home treatment. Details of this and other recommended revisions to the product literature are beyond the scope of the AusPAR.

RMP: educational materials

The sponsor plans to have demonstration kits for use in haemophilia centres and to have patient education material. The kits and materials have not been provided to the RMP Evaluation Section for review.

If these materials cannot be provided for review prior to approval, it will be a condition of registration that the materials must be provided for review and found acceptable by the RMP Evaluation Section prior to supply / launch of the product.

Proposed action

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

Request for ACPM advice

The Delegate proposed to seek general advice on this application from the Advisory Committee on Prescription Medicines (ACPM) and to request the committee provide advice on the following specific issue:

1. Can a weekly 65 IU/kg dosing strategy be endorsed, in routine prophylaxis?

Response from sponsor

The sponsors response to matters raised in the Delegate's overview are shown below:

In the Delegate's overview, it was noted that an updated RMP will be submitted at the same time as the pre ACPM response.

Biogen Idec response:

As requested, an updated RMP, with follow up questionnaires appended in an annex, has been developed and will be provided to the Delegate and RMP evaluator as requested at the same time as the Pre ACPM response is provided to TGA.

In the Delegate's Overview,'s , ACPM's advice is being sought on the following question:

- Can a weekly 65 IU/kg dosing strategy be endorsed, in routine prophylaxis?

Biogen Idec response:

Arm 2 of the pivotal Phase III study (997HA301) evaluated a dose of 65 IU/kg weekly. Due to the burden of frequent infusions, a significant proportion of subjects with severe haemophilia do not currently undertake prophylaxis. Additionally, weekly dosing with currently available FVIII concentrates has been advocated as an appropriate starting regimen [Feldman 2006¹⁸]. For these reasons, the randomised evaluation of the annualised bleeding rate (ABR) in the weekly dosing arm compared to the episodically treated arm was included in the study to provide important safety, efficacy, and PK data that would facilitate therapeutic decision-making for appropriate patients.

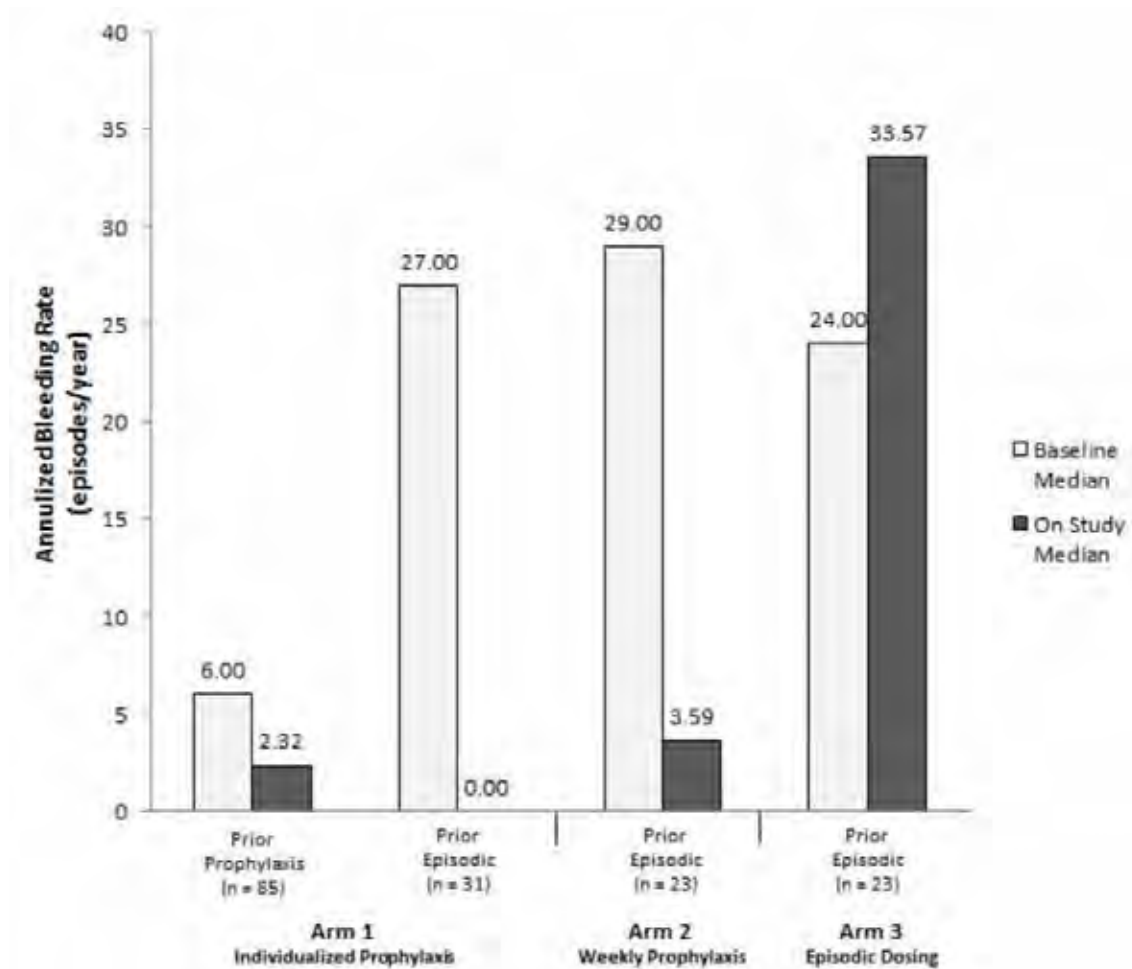
¹⁸ Feldman BM, et al. Tailored prophylaxis in severe hemophilia A: interim results from the first 5 years of the Canadian Hemophilia Primary Prophylaxis Study. *J Thromb Haemost.* 2006 Jun;4(6):1228-36.

PK evaluation following the 65 IU/kg dose in Arm 2 revealed a geometric mean time after dose when FVIII activity has declined to 1 IU/dL above baseline (Time 1%) of 5.249 days. The population PK modelling demonstrated that a dose of 65 IU/kg once weekly would maintain a trough above 1% in 26.7% of subjects. These data supported the conclusion that the weekly regimen could maintain subjects above the 1% target threshold for the majority of the dosing interval and a proportion of subjects above the target threshold for the entire dosing interval.

Consistent with the PK data, the efficacy evaluation for Arm 2 revealed that rFVIIIc administered at a dose of 65 IU/kg weekly, resulted in a significant reduction in ABR of 76% ($p < 0.001$) compared to the episodically treated arm. This result exceeded the predefined threshold for a clinically meaningful reduction in ABR of 50%. In addition, 17.4% of subjects in Arm 2 had no bleeding episodes on study. Importantly, this result was consistent with the pre study/on study evaluation demonstrating that patients being treated episodically can reduce their number of bleeding episodes with a weekly infusion of 65 IU/kg (Figure 2). As with all other FVIII regimens, subsequent adjustments can be made for patients who do not achieve their therapeutic goals on this starting regimen.

In summary, the Phase III study demonstrated that a weekly dosing regimen of 65 IU/kg results in significant reduction in ABR and is an appropriate starting regimen for patients unable or unwilling to infuse more frequently.

Figure 2: Study 997HA301. Number of Bleeding Episodes in the Prior 12 Months Compared With the On-Study Annualised Bleeding Rate, by Pre-Study FVIII Regimen



In the Delegate's Overview, it is noted that educational materials and demonstration kits have not been provided to TGA for review. If these materials cannot be provided for review

prior to approval, it will be a condition of registration that the materials must be provided for review and found acceptable by the RMP evaluation section prior to supply/launch of the product.

Biogen Idec response:

Biogen Idec plans to develop a number of educational materials for use by both health care professionals and by patients or patients' carers, per the requirement of the National Blood Authority (NBA) in Australia. A requirement of participation in the reimbursement by tender process (which is managed by NBA) is that the tenderers provide support for products supplied under the tender, including by making available documents which may include:

- Clinical educational materials or other informational materials related to the product and the use of the product, which are suitable for doctors, nurses, counsellors, laboratory staff, and other health care professionals
- Information which is suitable for use by patients and their carers.

Biogen Idec is therefore developing these materials in accordance with the requirements of the NBA to serve the needs of the haemophilia community as a whole. Biogen Idec therefore does not believe that TGA RMP evaluation section review or approval of these materials is warranted prior to supply.

The remainder of the sponsor's response relates to the Delegates' proposed revisions to product literature and is beyond the scope of the AusPAR.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The submission seeks to register a new chemical entity.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Eloctate powder for injection containing 250, 500, 750, 1000, 1500, 2000 and 3000 IU of Efmoroctocog alfa to have an overall positive benefit risk profile for the proposed indication;

Eloctate is a long acting antihaemophilic factor (recombinant) indicated in adults and children (≥ 12 years) with haemophilia A (congenital factor VIII deficiency) for:

- *control and prevention of bleeding episodes*
- *routine prophylaxis to prevent or reduce the frequency of bleeding episodes*
- *perioperative management (surgical prophylaxis)*

Eloctate does not contain von Willebrand factor, and therefore is not indicated in patients with von Willebrand's disease.

In making this recommendation the ACPM;

- Noted long term safety has not been established.
- Expressed concern that there is no safety data in children aged < 12 years.
- Noted no safety data in previously untreated patients (at higher risk of inhibitor development).
- Noted the risk of severe hypersensitivity reactions are not yet known.

Proposed conditions of registration:

The ACPM agreed with the Delegate on the proposed conditions of registration and specifically advised on the inclusion of the following:

- Submission to the TGA of reports from the ongoing paediatric studies as soon as they are available.
- Subject to satisfactory implementation of the RMP most recently negotiated by the TGA.
- Negotiation of PI and CMI to the satisfaction of the TGA.

Proposed PI/ CMI amendments:

The ACPM agreed with the Delegate to the proposed amendments to the PI and CMI.

Specific advice:

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

2. Can a weekly 65 IU/kg dosing strategy be endorsed, in routine prophylaxis?

ACPM agreed that the efficacy and safety data supported a weekly 65 IU/kg dosing strategy. This dosing strategy was consistent with existing practice using Factor VIII products registered currently.

The ACPM advised that the 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 Eloctate efmoctocog alfa (rhu) 250 IU, 500 IU, 750 IU, 1000 IU, 1500 IU, 2000 IU and 3000 IU powder for injection vial and diluent pre filled syringe for intravenous infusion, indicated for:

Eloctate is a long acting antihemophilic factor (recombinant) indicated in adults and children (≥ 12 years) with haemophilia A (congenital factor VIII deficiency) for:

- *control and prevention of bleeding episodes*
- *routine prophylaxis to prevent or reduce the frequency of bleeding episodes*
- *perioperative management (surgical prophylaxis)*

Eloctate does not contain von Willebrand factor, and therefore is not indicated in patients with von Willebrand's disease.

Specific conditions of registration applying to these goods

- The Australian Risk Management Plan Version 2, dated 16 May 2014, and any amendments agreed to or subsequent versions approved by the TGA's Office of Product Review (RMP Evaluation Section) must be implemented in Australia.
- It is a condition of registration that demonstration kits and patient education materials must be provided for review and found acceptable by the RMP Evaluation Section prior to launch of the product.

Details of additional specific conditions of registration applying to these goods including batch release conditions are beyond the scope of the AusPAR.

Attachment 1. Product Information

The Product Information approved for Eloctate at the time this AusPAR was published is at Attachment 1. For the most recent Product Information 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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