# Australian Public Assessment Report for Eftrenonacog Alfa

Proprietary Product Name: Alprolix

Sponsor: Biogen Idec Australia Pty Ltd

**November 2014**

TGA Health Safety Regulation

# About the Therapeutic Goods Administration (TGA)

· The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.

· The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.

· The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.

· The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.

· To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

# About AusPARs

· An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.

· AusPARs are prepared and published by the TGA.

· An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.

· An AusPAR is a static document, 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.

# Contents

# List of the most common abbreviations used in this AusPAR

| Abbreviation | Meaning |
|---|---|
| ACSOM | Advisory Committee on the Safety of Medicines |
| AE | Adverse Event |
| ARTG | Australian Register of Therapeutic Goods |
| AUC | Area Under the Curve (concentration versus time) |
| $AUC_{0-\infty}$ | Area Under the Curve (concentration versus time) for time 0-infinity |
| CMI | Consumer Medicine Information |
| $C_{max}$ | Maximum Concentration |
| $EC_{50}$ | Half maximal effective concentration |
| $ED_{50}$ | Half maximal effective dose |
| ECG | Electrocardiogram |
| EMA | European Medicines Agency |
| FIX | Factor IX |
| FIXFc | Eftrenonacog alfa |
| FDA | Food and Drug Administration |
| GLP | Good Laboratory Practice |
| GCP | Good Clinical Practice |
| h | Hour |
| Ig | Immunoglobulin |
| ICH | International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use |
| IV | Intravenous, intravenously |
| OPR | Office of Product Review |
| PI | Product Information |
| PK | Pharmacokinetic/s |

| Abbreviation | Meaning |
|---|---|
| PTP | Previously Treated Patient |
| PSUR | Periodic Safety Update Report |
| PUP | Previously Untreated Patient |
| rFIXFc | Recombinant Factor IX linked to the fusion protein (Fc) of immunoglobulin G; eftrenonacog alfa |
| RMP | Risk Management Plan |
| SAE | Serious Adverse Event |
| SDS PAGE | Sodium Dodecyl Sulphate Polyacrylamide Gel Electrophoresis |

# I. Introduction to product submission

## Submission details

| | |
|---|---|
| *Type of submission:* | New biological entity |
| *Decision*: | Approved |
| *Date of decision:* | 17 April 2014 |
| *Active ingredient:* | Eftrenonacog alfa |
| *Product name:* | Alprolix |
| *Sponsor's name and address:* | Biogen Idec Australia Pty Ltd<br>Suite 1, Level 5<br>123 Epping Road<br>North Ryde, NSW 2113 |
| *Dose form:* | Powder for injection and diluent |
| *Strengths:* | 250, 500, 1000, 2000 and 3000 International Units (IU) |
| *Container:* | Type 1 glass vial (powder) and prefilled syringe (diluent) |
| *Pack size:* | Single |
| *Approved therapeutic use:* | *Alprolix is a long-acting anti-haemophilic factor (recombinant) indicated in adults and children (≥ 12 years) with haemophilia B (congenital factor IX deficiency) for*<br><br>· *the control and prevention of bleeding episodes;*<br>· *routine prophylaxis to prevent or reduce the frequency of bleeding episodes;*<br>· *perioperative management (surgical prophylaxis)* |
| *Route of administration:* | Intravenous (IV) |
| *Dosage:* | Refer to the approved Product Information (PI; Attachment 1) |
| *ARTG numbers:* | 209227 (250 IU), 209223 (500 IU), 209224 (1000 IU), 209225 (2000 IU) and 209226 (3000 IU) |

## Product background

This AusPAR describes the application by Biogen Idec Australia Pty Ltd (the sponsor) to register the new biological entity, eftrenonacog alfa (Alprolix), a recombinant form of coagulation Factor IX (rFIX) covalently linked to the fusion protein (Fc) of immunoglobulin G (IgG), which confers prolonged clotting activity.

*Alprolix is proposed for IV use in adults and adolescents (≥ 12 years) with haemophilia B: (i) to control and prevent bleeding episodes; (ii) for routine prophylaxis against frequent bleeding episodes and (iii) for surgical prophylaxis.*

Australian clinical guidelines for treatment of haemophilia B include evidence based clinical practice guidelines for the use of recombinant and plasma derived Factor VIII (FVIII) and FIX products[1]. Therapy rests on FIX replacement.

Currently registered products for treatment of haemophilia B include:

· Plasma derived FIX

   – MonoFIX-VF

· Recombinant FIX

   – nonacog alfa [BeneFIX]

   – nonacog gamma [Rixubis]

Factor IX in these products has a half-life of approximately 24 h (compared to approximately 82 h for Alprolix), resulting in broadly similar dosing frequencies for registered products, as follows:

**Table 1: Comparison of registered product dosage and proposed dosage for Alprolix**

| | MonoFIX-VF | BeneFIX | Rixubis | Alprolix (proposed) |
|---|---|---|---|---|
| Bleeding treatment | 1 dose per day (minor bleeding) <br><br> 1-2 per day (moderate to severe bleeding) | 1-2 per day | 1 per day except for life threatening bleeding (1-3 per day) | *1 per two days (minor and moderate bleeding)* <br><br> *After 6-10 h then every 24 h (major bleeding)* |
| Surgical prophylaxis | Loading dose then 1-2 per day | 1-2 per day | 1 per day (minor) <br><br> 1-3 per day (major) | *1 per one-two days (minor)* <br><br> *After 6-10 h then every 24 h (major)* |
| Routine prophylaxis | Twice weekly | Two to three times per week | Twice weekly | *Weekly (50 IU/kg) or every 10-14 days (100 IU/kg)[2]* |

The general approach is to modify dosage regimens (for example dosage intervals, doses) based on individual factors.

Romiplostim, aflibercept, etanercept and abatacept are examples of registered products that are fusion proteins combining the Fc fragment of IgG1 and another active molecule. Long plasma residency time is one purported advantage of such peptibodies (peptide plus antibody).

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[1] Australian Health Ministers' Advisory Council (2006). National Blood Authority (NBA)/Australian Haemophilia Centre Directors' Organisation (AHCD). Evidence-based clinical practice guidelines for the use of recombinant and plasma-derived FVIII and FIX Products. June 2006.
[2] The finally agreed dose for routine prophylaxis is 50 IU/kg once weekly or 100 IU/kg once every 10 days.

Alprolix for *"the control and prevention of haemorrhagic episodes in patients with haemophilia B (congenital factor IX deficiency or Christmas disease), including the control and prevention of bleeding in surgical settings."* was granted orphan drug status by the TGA on 20 September 2012.

Eftrenonacog alfa is referred to as rFIXFc in this AusPAR.

### Regulatory status

Alprolix received initial registration on the Australian Register of Therapeutic Goods (ARTG) on 1 May 2014.

At the time this application was considered by the TGA, similar applications had been submitted to the USA (December 2012), Canada (March 2013), Japan (September 2013) and South Africa (December 2013), and were planned for New Zealand (2014) and the European Union (in 2015).

### 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 <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

# II. Quality findings

### Drug substance (active ingredient)

### Structure

The recombinant coagulation Factor IX covalently linked to the fusion protein (rFIXFc; eftrenonacog alfa) is a fully recombinant fusion protein consisting of full length human coagulation FIX covalently linked (no linker sequence) to the Fc domain of human IgG1. The structure of rFIXFc consist of two protein subunits, FIXFc single chain (FIXFc-sc) (641 amino acids) and Fc single chain (Fc-sc) (226 amino acids) as shown in Figure 1. The FIXFc-sc and Fc-sc are bound together through two disulfide bonds in the hinge region of Fc. The molecular weight of rFIXFc is approximately 98 kDa.

**Figure 1: Schematic structure of rFIXFc**
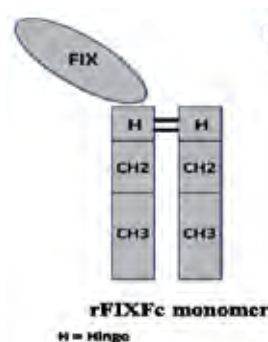


The Fc region of IgG1 binds to neonatal Fc receptor (FcRn), which is part of a naturally occurring pathway that delays lysosomal degradation of immunoglobulins by cycling them back into circulation. The Fc is responsible for the long plasma half-life.

The rFIXFc single chain is expressed as pre-pro-protein.

In the coagulation cascade in vivo, FIX is cleaved by FXIa, which removes the activation peptide from FIX to generate FIXaβ in one of the routes to clot formation (the intrinsic pathway). Factor XIa activates FIXFc by cleaving the protein twice, first at Arg145 leading to the formation of the FIXαFc which is inactive, and then at Arg180 resulting in complete removal of the activation peptide (ACT PEP) and formation of the active FIXaFc form (FIXaβ). An illustration of the FXIa activation of FIX is shown below.
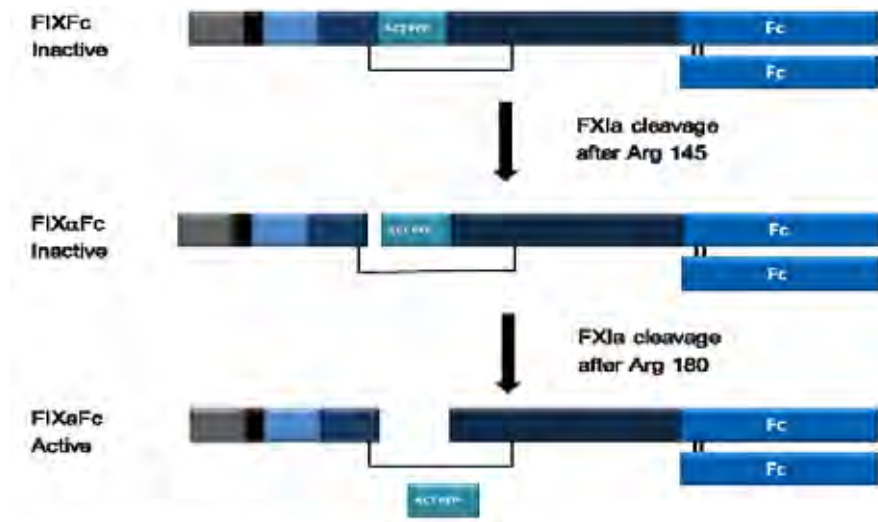
**Figure 2: Schematic illustration of FIXFc activation**



The inter-subunit (or inter-chain) disulphide bonds are shown with solid lines.

## Manufacture

The drug substance is manufactured at the bioreactor scale. One working cell bank vial is used to produce one discrete batch of rFIXFc drug substance.

Cell banking processes are satisfactory.

All viral and prion safety issues have been addressed, including use of animal derived excipients, supplements in the fermentation process and in cell banking.

## Physical and chemical properties

The FIX portion of eftrenonacog alfa has similar structural and functional characteristics as endogenous FIX. The structural characterisation of rFXIII has confirmed the theoretical structure. The characterisation included an assessment of subunit composition, primary sequence, post-translational modifications, charge heterogeneity, carbohydrate, secondary and tertiary structure, in vitro biological activity and activation kinetics by FXIa. Additional functional assays (the ability to form an active tenase [Xase] complex, inhibition by antithrombin III, and interaction with phospholipids) for 3 drug product batches also have performed using commercially available recombinant FIX (BeneFIX) as a control. The results have shown that the functional characteristics of rFIXFc were consistent with the expected FIX and Fc functionalities. The coagulation activity and potency to bind neonatal Fc receptor FcRn are consistent across all the drug substance batches.

The manufacturing process has been targeted at reducing the level of impurities during manufacture and storage. The test for Size Exclusion Chromatography, Sodium Dodecyl Sulfate Polyacrylamide Gel Electrophoresis (SDS-PAGE; non-reducing and reducing), activated rFIXFc, Host Cell Protein, endotoxins and bioburden are retained in routine batch release testing.

## Specifications

Appropriate validation data have been submitted in support of the test procedures for the proposed specifications, which control identity, content, 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 were submitted to support shelf life, and data were also submitted to support storage of the drug substance after thawing.

## Drug product

## Formulation

The rFIXFc is formulated as a sterile, non-pyrogenic, single use, preservative free, white to off-white, lyophilized powder for IV administration in a single use vial. Each vial contains nominally 250, 500, 1000, 2000 or 3000 International Units (IU) of rFIXFc and is presented with a kit containing a vial adapter and diluent syringe prefilled with 5 mL of 0.325% sodium chloride.

The rFIXFc drug product is lyophilised in a Type 1 glass vial, closed with a Teflon coated butyl rubber lyophilisation stopper and an aluminium flip-off crimp seal that varies in colour with dosage strength.

## Manufacture

Information was evaluated on the manufacturing process, including sterilisation 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 osmolality, endotoxin, and coagulation activity per vial.

## Stability

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. Photostability data demonstrate the product is not photostable. Labelling warning are in place to reflect this.

In-use stability data have also been submitted. The reconstituted product stored for this period is not affected by normal room lighting.

The sponsor has proposed alternative transport conditions with registered temperature deviations. These are not supported by the supplied data and are not accepted.

The product should be transported at the recommended storage temperature only.

**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, 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.

There are no unresolved Module 3 issues.

The Module 3 evaluators recommended that Alprolix (eftrenonacog alfa) 250, 500, 1000, 2000 and 3000 IU powder for injection vial plus diluent 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

The quality of the nonclinical dossier for Alprolix was generally satisfactory. Most submitted studies were performed according to Good Laboratory Practice (GLP) and followed protocols consistent with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) Guideline *S6 (R1) – preclinical safety evaluation of biotechnology-derived pharmaceuticals* (CHMP/ICH/731268/1998). There is currently another recombinant human FIX product with marketing approval in Australia, BeneFIX (nonacog alfa, rch), also indicated for control and prevention of bleeding in haemophilia B patients. Because the one factor distinguishing Alprolix over BeneFIX is its prolonged clotting activity arising from the presence of the Fc fusion protein, a focus of this submission was to compare the pharmacodynamic (clotting efficacy) and pharmacokinetic (PK) attributes (elimination half-life) of the two products. All animal studies used the clinical route of administration (IV). A number of repeat dose toxicity studies were conducted in rats and monkeys, regarded as species pharmacologically responsive to rFIXFc (expression of the FcRn receptor which binds with Fc is conserved across many species[3]). Determination of safety pharmacology parameters were also intended to be incorporated into these studies. As such, no dedicated safety pharmacology studies on rFIXFc were conducted. All repeat dose toxicity studies were also monitored for antibody development. In addition, studies on local tolerance and the thrombogenic potential of rFIXFc were performed in rabbits.

## Comparability of manufactured batches

A number of nonclinical comparability studies were conducted on different batches of rFIXFc (for example different manufacturing cell lines, liquid versus lyophilised formulations, drug substance scale), which demonstrated comparable clotting activities, PK profiles, tolerance and thrombogenic potential. These batches were also used in the clinical studies.

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[3] Roopenian, DC, Akilesh S. FcRn: the neonatal Fc receptor comes of age. *Nat. Rev. Immunol.* 2007:7(9);715-725

## Pharmacology

### Primary pharmacology

A number of in vitro and in vivo primary pharmacology studies were submitted that examined efficacy and activity of rFIXFc. Effects of rFIXFc were compared with BeneFIX (recombinant human FIX without Fc subunit). Using human platelets, rFIXFc and BeneFIX both formed the tenase complex (that is, interacted with Factor VIIIa) and generated activated Factor X (FXa) to similar extents. Activity was slightly lower for rFIXFc than BeneFIX (as FXIa activation: 89% compared to 97%, respectively) but this was attributed to a stoichiometric consideration related to the higher molecular weight of rFIXFc compared to BeneFIX. Surface Plasmon Resonance techniques confirmed binding between rFIXFc and the FcRn from various species (receptor affinity calculated as half maximal effective concentration ($EC_{50}$): rat 49 nM, monkey 318 nM and human 235 nM), thus validating the use of rats and monkeys for the toxicity studies.

For the in vivo studies, the acute and prophylactic efficacies of rFIXFc and BeneFIX were compared against induced bleeds in mouse and dog models of haemophilia B (Hem B mice and Hem B dogs, which are FIX deficient). Clotting times in an acute bleeding mouse model were similar for rFIXFc and BeneFIX; although onset of activity was quicker for BeneFIX than for rFIXFc. Sustained clotting activity was evident with rFIXFc at 96 h but was below the limit of detection with BeneFIX by this time. With respect to prophylaxis, both rFIXFc and BeneFIX caused dose dependent increases in re-bleeding times (reflecting improvements in clotting function) in HemB mice, which correlated to improved survival rates and higher plasma FIX levels, with half maximal effective dose ($ED_{50}$) values extrapolated from survival rates (rFIXFc: 17.8 IU/kg; BeneFIX: 15.4 IU/kg). Similarly, Hem B dogs that received rFIXFc (140 IU/kg, IV) demonstrated sustained clotting activity at up to 144 h post dose, with clotting activity returning to pre-dose levels by 168 h.

### Secondary pharmacodynamics and safety pharmacology

The sponsor did not conduct any secondary pharmacology studies or dedicated safety pharmacology investigations. Since rFIXFc is intended as a replacement therapy for restoring deficient FIX to normal levels, secondary pharmacology studies were not deemed necessary. Effects on the cardiovascular system were assessed in the GLP repeat dose toxicity studies in cynomolgus monkeys. While no treatment related effects on heart rate or electrocardiogram (ECG) were reported in either the 5 week or 27 week study, actual details were not provided with the studies and were based on narrative assurances provided in the veterinarian report. Nevertheless, in the repeat dose toxicity studies, which the evaluator considered did not address core safety pharmacology systems, there were no overt treatment related effects that would suggest a specific effect on organ systems. The potential for thrombus formation in rabbits was low with rFIXFc treatment being comparable to or less than that seen with BeneFIX and saline.

### Pharmacokinetics

In mice and rats different PK profiles of rFIXFc and BeneFIX were demonstrated with elimination half-lives and plasma levels (as Area Under the Concentration versus Time Curve; AUC) substantially higher in the rFIXFc treated cohorts than in animals that received BeneFIX. On the other hand, half-lives of rFIXFc and BeneFIX were similar in mice that lacked expression of the FcRn receptor (FcRn KO), confirming a role of this receptor in the prolonged half-life seen with rFIXFc. Transgenic mice expressing human FcRn also had a prolonged half-life with rFIXFc, suggesting this will be seen in patients. Elimination half-lives in animal species (23 to 60 h; at least on Day 1) were shorter than those seen in patients (96 to 110 h). Plasma concentrations of rFIXFc (as either maximum concentration

($C_{max}$) or the AUC for time 0 to infinity, ($AUC_{0-\infty}$) were dose proportional in both rats and monkeys and were similar in males and females. Indicative of antibody development, at higher doses of rFIXFc, AUC values and elimination half-lives were lower in these species with repeat dosing; on the last sampling day, half-life had decreased to 16 to 18 h in rats and 2 h in monkeys.

The sponsor did not conduct any studies on the distribution of rFIXFc, which is acceptable for a clotting factor product not expected to accumulate in different tissue compartments. Consistent with this, and typical for a FIX product, the volume of distribution was less than total body water in all tested animal species, suggesting limited extravascular distribution. Similarly no studies on metabolism or excretion of rFIXFc were provided either, since its degradation results in small peptides or amino acids. Thus, these omissions are acceptable and consistent with ICH S6 (R1) guideline[4] recommendations.

*Conclusion:* As in human subjects, a prolonged elimination half-life of rFIXFc was seen in all animal species used in the toxicity studies (at least for the first day of sampling), thus supporting the use of these animals for the safety assessment. However, as would be anticipated for a recombinant human protein, the development of anti-rFIXFc antibodies reduced the half-life of rFIXFc in both species used in the repeat dose toxicity investigations, which is not unexpected and may not have clinical relevance. However, the lower exposures seen with repeat dosing may somewhat limit the interpretability of negative findings in the repeat dose toxicity studies.


## Toxicology


### Repeat dose toxicity

Four repeat dose studies (one a non-GLP pilot study) were submitted by the sponsor to assess the potential toxicities of rFIXFc in rats and cynomolgus monkeys. These studies were up to 4 weeks and 27 weeks, respectively, and included protocols for measuring antibodies that developed over the course of the treatment period. The duration of the pivotal study in monkeys is acceptable for a chronically used biotechnology product (ICH S6 (R1)). The clinical route (IV) was used in all GLP studies. The dosing regimen used in the monkey studies (once weekly) is similar to that recommended for routine prophylaxis. While dosing was every 4 days in the pivotal rat study, this is considered acceptable, given the shorter half-life of rFIXFc in this species compared with patients.

### *Relative exposure*

The proposed recommended dose in haemophilia B patients depends on clinical need, with a lower dose administered for routine prophylaxis (50 IU/kg, IV once per week) compared with acute need such as major surgery (100 IU/kg, IV, per day for first 3 days post procedure). Since long term prophylaxis is likely to be the more typical use, relative exposure comparisons are based on the highest routine dose used in the clinical studies: 100 IU/kg, IV.

In the nonclinical overview the sponsor cited safety margin values using $C_{max}$ comparisons (from a single dose study), on the basis that peak plasma FIX concentrations are a critical factor in controlling and preventing bleeding episodes. However, as a replacement product, particularly since the distinguishing feature of rFIXFc is its extended half-life and pharmacological action, it is the view of the evaluator that trough levels of FIX are more relevant as these determine the minimum conditions in which normal clotting activity is maintained. Ideally, comparisons should be based on AUC values but since sampling

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[4] CHMP/ICH/731268/1998. ICH Topic S6 (R1). Preclinical safety evaluation of biotechnology-derived pharmaceuticals.

intervals used in the animal studies differed (rat: 0 to 144 h post dose; monkey: 0 to 168 h post dose; human: 0 to 240 h post dose), this was not an ideal comparison and thus dose comparisons (IU/kg) were used instead. Ratios based on $C_{max}$ are also listed to compare with dose comparisons.

Dose ratios of the highest tested clinical dose for routine prophylaxis (100 IU/kg) against the highest doses used in the animal studies (1000 and 1750 IU/kg) were adequate: 10 and 17.5 fold the clinical dose in monkeys and rats, respectively.

**Table 2: Relative exposure in repeat dose toxicity studies**

| Species | Study duration | Dosage regimen | Dose IU/kg IV | Weekly dose IU/kg IV | $C_{max}$ µg/mL^ | Exposure ratio Dose | $C_{max}$ |
|---|---|---|---|---|---|---|---|
| **Rat*** SD | 4 weeks | every 4 days | 50 | 87.5 | 6.03 | 0.87 | – |
| | | | 200 | 350 | 18.4 | 3.5 | – |
| | | | 1000 | 1750 | 138 | 17.5 | – |
| **Monkey** Cynomolgus | 5 weeks | weekly | 50 | 50 | 6.5 | 0.5 | 0.4 |
| | | | 200 | 200 | 41.8 | 2 | 2.7 |
| | | | 1000 | 1000 | 236 | 10 | 15 |
| | 27 weeks | weekly | 50 | 50 | 8.6 | 0.5 | 0.6 |
| | | | 200 | 200 | 50.3 | 2 | 3.3 |
| | | | 1000 | 1000 | 302.5 | 10 | 20 |
| **Human** Hem B patients | Single dose | (Study SYN-FIXFc-07-001) | 100 | 100 | 15.4 | – | – |

*Because rats were dosed once every 4 days doses converted to weekly estimate values by dividing by 4 and multiplying by 7; ^values from the last sampling day (rats: Day 29; monkeys Day 30 and Day 183), shown as average male and female values.

**Major toxicities**

Repeated doses of rFIXFc were well tolerated in both animal species used in the toxicity studies: rats and cynomolgus monkeys. No deaths were observed in any of the studies and there were no overt treatment related clinical signs. In the longer duration monkey study, clinical signs consistent with a hypersensitivity reaction and likely associated with antibody development were noted, such as swelling of nose/muzzle, reddening of ears and genitalia, swelling of forelimb, which were transient and were not coincidental with gross pathological or histopathological changes. The data indicate a potential for hypersensitivity reactions during clinical use.

Antidrug antibodies were detected in monkeys that received weekly doses of rFIXFc for 27 weeks. Onset of development was earliest in the highest dose treated animals (1000 IU/kg,

IV) with a significant majority of animals from this group positive for antibodies by Day 29. Characterisation of the antibodies determined that they targeted different regions of the rFIXFc protein (that is the intact rFIXFc entity, the Fc moiety or the rFIX moiety). The clinical relevance of anti-drug antibody production in animals is uncertain, as it is not always predictive of the situation in human subjects. The potential for antibody production and its effect on rFIXFc exposures, as well as the potential to affect the activity of other FIX products, needs to rely solely on clinical data.

## Genotoxicity and carcinogenicity

No genotoxicity studies with rFIXFc were submitted which is acceptable given the nature of the product (protein) and the absence of a chemical linker (see ICH S6 (R1)). The absence of carcinogenicity studies is also acceptable on the grounds that ICH guidance regards standard carcinogenicity studies as inappropriate for ascertaining the carcinogenicity of biotechnology derived products.

## Reproductive toxicity

The sponsor did not conduct reproductive toxicity studies on rFIXFc nor do they plan to conduct any in the future. This is acceptable in view of the fact that males with a sex linked disease are the intended patient population and exposure to females during pregnancy and embryofetal development is remote. The sponsor highlighted the lack of test article findings on the male reproductive organs of rats and monkeys from the repeat dose toxicity studies as evidence that fertility was unlikely to be affected. Other FIX products have been approved for registration without studies assessing reproductive and developmental toxicity.

### *Pregnancy classification*

The sponsor did not nominate a pregnancy category for rFIXFc. Whilst the patient population affected by haemophilia B and intended to use rFIXFc 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. Most of the other recombinant clotting factor substances, including recombinant FIX (BeneFIX), have been assigned category B2[5], on the basis that no animal reproductive studies have been conducted to determine effects on fetal development. Thus, rFIXFc should also be assigned Category B2[6].

## Local tolerance

In rabbits, a slightly higher grade of erythema was observed following IV administration of 566 IU/mL rFIXFc (slightly higher than the clinical dose) compared with saline, but no evidence of tissue damage. There was no significant difference between treated and control sites following paravenous injection to rabbits. Overall, local reactions are predicted to be minimal during clinical use.

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[5]Definition of category B2 for use of medicines in pregnancy: *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.*

[6] The Delegate subsequently assigned eftrenonacog alfa 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.

**Paediatric use**

Although rFIXFc is proposed for use in adults and adolescents (≥ 12 years old), no studies in juvenile animals were performed. There were no significant or notable effects noted in the repeat dose toxicity studies to raise concern about use in a younger patient population.

**Nonclinical summary and conclusions**

- The quality of the nonclinical submission was generally satisfactory, with pertinent studies performed under GLP conditions, meeting most ICH guideline recommendations relevant for biotechnology derived therapeutic products. The clinical route (IV) was used and animal models were appropriate and responsive to rFIXFc.

- rFIXFc was shown to have comparable clotting activity to the comparator BeneFIX (rFIX). Affinity for the FcRn receptor was demonstrated with rat, monkey and human FcRn receptors. In animal models of haemophilia B (mice and dogs), sustained clotting activity correlated with sustained plasma FIX levels. Both bleeding and prophylactic models were used, thus supporting the proposed indication.

- Safety pharmacology assessments were not comprehensive. Nonetheless, this is not considered a major deficiency, given the nature of the drug.

- The elimination half-life and plasma FIX levels (as AUC) were higher for rFIXFc than BeneFIX across all tested species (mice and rats). Confirming involvement of Fc in conferring longer activity of rFIXFc, FcRn knockout mice had comparable elimination half-lives for rFIXFc and BeneFIX. Shorter half-lives and lower exposures (AUC) were seen in rats and monkeys with repeat dosing, which correlated with anti-drug antibody production. No studies on the distribution, metabolism or excretion of rFIXFc were submitted, which is acceptable.

- rFIXFc was well tolerated in repeat dose toxicity studies in rats and monkeys with minimal changes noted at doses significantly higher than the routine clinical dose. The only notable effects were signs of a hypersensitivity reaction (swelling of nose or muzzle, reddening of ears and genitalia, and swelling of forelimb) in monkeys, which may have correlated with antibody production. Antigenicity was a consistent feature of the chronic dose studies, which reduced circulating FIXFc levels. The clinical relevance of the antibody and hypersensitivity reactions is uncertain, but should at this stage be considered as possible.

- The thrombogenic potential of rFIXFc was no greater than BeneFIX or saline.

- Genotoxicity and carcinogenicity studies on rFIXFc were not conducted, which is consistent with ICH guidelines for biotechnology derived therapeutic products.

- Local reactions to rFIXFc when tested in rabbits using the intravenous and paravenous routes were minimal. Significant injection site reactions are not predicted during clinical use.

- Overall there are no nonclinical objections to registration.

Details of the nonclinical evaluator's recommended revisions to the draft PI are beyond the scope of this 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

Eftrenonacog alfa is a fusion protein in which a rFIX molecule is covalently linked to the Fc fragment of an IgG1 molecule. The proposed indication is:

*Alprolix is a long-acting anti-haemophilic factor (recombinant) indicated in adults and children (≥ 12 years) with haemophilia B (congenital factor IX deficiency) for:*

·   *Control and prevention of bleeding episodes.*

·   *Routine prophylaxis to prevent or reduce the frequency of bleeding episodes.*

·   *Perioperative management (surgical prophylaxis).*

The product is presented as a lyophilised powder for injection in the following vial sizes: 250, 500, 1000, 2000 or 3000 International Units (IU). Each vial is supplied with 5 mL of solvent in a pre-filled syringe.

The product is intended for IV administration only.

There are several dosage regimens proposed, depending on the clinical scenario.

## Clinical rationale

The current standard treatment of congenital FIX deficiency is based on the use of replacement FIX therapy. Two replacement therapy products are currently registered in Australia:

·   Plasma derived FIX (MonoFIX-VF).

·   Recombinant FIX (nonacog alfa; BeneFIX).

The FIX contained in these products has a half-life of approximately 24 h. For the treatment of bleeding episodes and for surgical prophylaxis it is recommended that dosing be repeated every 12 to 24 h. For routine prophylaxis, dosing is recommended twice per week.

The rationale for the development of eftrenonacog alfa (Alprolix) is that combining the rFIX molecule with the Fc fragment of the IgG1 molecule will result in a prolonged half-life, with less frequent dosing required. The draft PI states that eftrenonacog alfa has an elimination half-life of 82 h and the recommended dosage interval for the treatment of bleeding episodes and surgical prophylaxis is up to 48 h. The recommended initial dosage interval for routine prophylaxis is up to 14 days.

The prolonged half-life of the molecule occurs because of binding of the Fc fragment with the neonatal Fc receptor for IgG (FcRn). FcRn derives its name through its role in the transfer of IgG from mother to foetus. However, it is also expressed in several adult human tissues and is believed to bind with the Fc fragment of IgG and prevent IgG degradation. FcRn is therefore believed to be responsible for the prolonged half-life of IgG compared to other endogenous proteins.

Currently registered products that are fusion proteins combining the Fc fragment of an IgG1 molecule with another active molecule include romiplostim and etanercept.

## Orphan drug designation

The product was granted orphan drug status by the TGA on 20 September 2012. The orphan indication granted was:

> *"... the control and prevention of haemorrhagic episodes in patients with haemophilia B (congenital factor IX deficiency or Christmas disease), including the control and prevention of bleeding in surgical settings."*

The indication proposed for registration is narrower than that granted in the orphan designation, in that children aged less than 12 years have been excluded.

The Haemophilia Foundation of Australia estimates that there are approximately 2,800 subjects with haemophilia in Australia[7]. Approximately 15-20% of haemophilia subjects have haemophilia B[8] and therefore the prevalence of the condition in Australia would be approximately 420 to 560 subjects.

## Guidance

The following European Medicines Agency (EMA) guidelines, which have been adopted by the TGA, are considered relevant to the current application.

- Guideline on the Clinical Investigation of the Pharmacokinetics of Therapeutic Proteins (CHMP/EWP/89249/2004); 2007.

- Points to Consider on Application with 1. Meta-Analyses; 2. One Pivotal Study (CPMP/EWP/2330/99); 2001.

- Note for Guidance on the Clinical Investigation of Recombinant Factor VIII and IX Products (CPMP/BPWG/1561/99); 2000.

In Europe, the 2000 guideline on recombinant Factor VIII and IX products has been superseded by a new guideline specific for Factor IX products:

- Guideline on clinical investigation of recombinant and human plasma-derived factor IX products (EMA/CHMP/BPWP/144552/2009); 2011.

This later guideline came into effect in Europe in February 2012, but had not been formally adopted in Australia at the time the CER was prepared[9].

## Contents of the clinical dossier

The submission contained the following clinical information:

- Module 2
  - Clinical overview, summary of biopharmaceutic studies and analytical methods, summary of clinical pharmacology, summary of clinical efficacy and summary of clinical safety.

- Module 5
  - A full study report of one open-label, Phase I/IIa study (SYN-FIXFc-07-001) that examined the safety and pharmacokinetics of escalating single doses of rFIXFc in a total of 14 subjects with haemophilia B.
  - A full study report of one open-label, Phase III pivotal efficacy and safety study (998HB102) that examined the PK, efficacy and safety of rFIXFc in a total of 123 subjects with haemophilia B.
  - One population PK analysis of PK data collected in the above two studies.
  - Brief safety reports from two ongoing studies (9HB02PED and 9HB01EXT). These reports included limited information regarding serious adverse events and adverse events of special interest.

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[7] Haemophilia Foundation Australia. Haemophilia, July 2013 Available from: <http://www.haemophilia.org.au/documents/item/2040>
[8] Srivastava A, Brewer AK, Mauser-Bunschoten EP et al. Treatment Guidelines Working Group The World Federation Of Hemophilia. Guidelines for the management of hemophilia. *Haemophilia*. 2013;19:e1-e47
[9] EMA/CHMP/BPWP/144552/2009 was adopted by the TGA effective 1 June 2014

– Literature references.

## *Paediatric data*

The pivotal study in the submission included previously treated patients (PTPs) aged 12 years and over and the indication sought by the sponsor is restricted to this group. One of the ongoing studies (9HB02PED) is a trial of the product in PTPs aged less than 12 years. It is planned to enrol at least 20 subjects and completion is expected by second quarter (Q2) 2015. Another study is planned in previously untreated patients (PUPs) aged less than 18 years, with completion expected in Q2 2019.

> **Evaluator comment:** EMA *Guideline on clinical investigation of recombinant and human plasma-derived factor IX products* (EMA/CHMP/BPWP/144552/2009), 2011, on recombinant Factor VIII and IX products, which has been adopted by the TGA, indicates that the submission of paediatric data can be delayed until after initial marketing approval. The absence of data on children aged less than 12 years of age in this submission is therefore not considered a deficiency in the application.

## *Good clinical practice*

The study reports for the completed studies included assurances that they had been conducted in accordance with applicable guidelines including the ICH Guideline on Good Clinical Practice (GCP) and the ethical principles outlined in the Declaration of Helsinki.

## Pharmacokinetics

### Studies providing pharmacokinetic data

Pharmacokinetics data were collected in both SYN-FIXFc-07-001 and 998HB102, and a population PK analysis was also conducted on these data.

None of these pharmacokinetic studies had deficiencies that excluded their results from consideration. Both studies were conducted in subjects with FIX deficiency (haemophilia B) and hence there were no studies in healthy volunteers.

### Pharmacokinetics in haemophilia B subjects

#### *Absorption and bioavailability*

Recombinant FIXFc is only administered IV and by definition has 100% absorption and bioavailability. The time to maximal concentration ($T_{max}$) occurred immediately after the completion of the infusion.

#### *Incremental recovery*

The incremental recovery of rFIXFc was 0.92 IU/dL for every 1.0 IU/kg administered. The incremental recovery of BeneFIX was 0.95 IU/dL.

> **Evaluator comment:** Factor IX replacement products generally have an incremental recovery of approximately 1.00 IU/dL for every 1.0 IU/kg administered[10]. The value of 0.92 for rFIXFc is consistent with this. However, BeneFIX is considered to have a lower recovery than plasma-derived FIX[11]. The value for incremental recovery in adults quoted in the Australian PI for Benefix is 0.72 IU/dL for every 1.0 IU/kg administered. As the recovery values for rFIXFc and

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[10] Srivastava A, Brewer AK, Mauser-Bunschoten EP et al. Treatment Guidelines Working Group The World Federation Of Hemophilia. Guidelines for the management of hemophilia. *Haemophilia*. 2013;19:e1-e47
[11] Franchini M, Frattini F, Crestani S et al. Treatment of hemophilia B: focus on recombinant factor IX. *Biologics: Targets and Therapy* 2013;7:33–38.

Benefix in this study were comparable, rFIXFc may also have a lower recovery than plasma-derived FIX.

*Dose proportionality*

Mean $C_{max}$ and AUC increased in an approximately dose proportional manner for both FIX activity and rFIXFc antigen, over the dose range of 25 to 100 IU/kg.

*PK during multiple dosing*

There was no alteration in the PK of rFIXFc after 26 weeks of dosing using a prophylaxis regimen.

*Distribution*

·  In the conventional PK studies, the volume of distribution at steady state ($V_{ss}$) varied between 227 and 314 mL/kg (16 to 22 L for a 70 kg individual). In the population PK analysis the estimated $V_{ss}$ was 271 mL/kg.

·  There were no clinical data submitted on plasma protein binding, erythrocyte distribution or tissue distribution.

   **Evaluator comment:** The guideline on PK of therapeutic proteins adopted by the TGA[12] states that "... binding capacity to plasma proteins should be studied when considered relevant". It contains no recommendations regarding the need to measure distribution to tissues. The absence of data on other distribution parameters is not considered a deficiency in the submission.

*Metabolism and excretion*

·  There were no clinical data in the submission regarding the routes of metabolism and excretion of rFIXFc.

   **Evaluator comment:** According to the guideline on PK of therapeutic proteins, the elimination of large proteins can be predicted to occur through catabolism by proteolysis.

*Clearance and half life*

·  Following a single intravenous dose of rFIXFc, clearance was measured as 3.19 mL/h/kg. This equates to 3.72 mL/min for a 70 kg individual.

·  In the same study, half-life (of FIX activity) was measured as 82.1 h. The half-life of rFIXFc antigen was longer (up to 145 h), probably due to the greater sensitivity of the rFIXFc Antigen assay compared to the FIX activity assay.

*Intra- and inter-individual variability of pharmacokinetics*

Both inter-individual and intra-individual variability in PK parameters appeared modest. In the population PK analysis, weight was the only covariate that demonstrated an effect on the PK of rFIXFc. All the dosage regimens proposed by the sponsor are weight adjusted.

**Pharmacokinetics in other special populations**

·  There were no clinical data on the effect of impaired hepatic

·  There were no clinical data on the effect renal function on the PK of rFIXFc.

   **Evaluator comment:** Renal clearance is unlikely to be significant for large proteins such as rFIXFc. Hence the absence of PK data in subjects with renal impairment is not considered to be a deficiency in the submission.

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[12] European Medicines Agency. *Guideline On The Clinical Investigation Of The Pharmacokinetics Of Therapeutic Proteins* (CHMP/EWP/89249/2004); 2007.

· In the population PK analysis, age, race, blood type or FIX genotype did not affect the PK of rFIXFc.

## Pharmacokinetic interactions

The submission contained no clinical data on interactions.

## Evaluator's conclusions on pharmacokinetics

The PK of rFIXFc have been adequately characterised, given the rarity of haemophilia B and the fact that rFIXFc is a large protein. In addition, the data generated meet the requirements for PK data laid down in the *Guideline on clinical investigation of recombinant and human plasma-derived factor IX products* (EMA/CHMP/BPWP/144552/2009) for haemophilia B.

## Pharmacodynamics

Factor IX activity was measured in both the submitted studies. In haemophilia studies this is generally considered to be a pharmacokinetic endpoint and results have therefore been described in the section on *Pharmacokinetics* (above).

In Study 998HB102, global haemostasis assays were performed, including an exploratory thrombin generation assay and, in some sites, whole blood rotation thromboelastometry. The results were not included in the submitted study report.

No other pharmacodynamic data were submitted.

## Dosage selection for the pivotal study

The doses chosen for prophylaxis and episodic treatment arms of the pivotal study (998HB102) were based on the results of the Phase I/IIa study (SYN-FIXFc-07-001). The target threshold of the prophylaxis and episodic treatment arms was to maintain FIX activity above 1% for at least 7 days. Based on the results from the Phase I/IIa study, the mean and median FIX activity on Day 7 with 50 IU/kg would be 2.55% and 1.89% above baseline, respectively. Also, over 70% of the population would have FIX activity of 1% above baseline on Day 7.

Doses selected for treatment for bleeding episodes in all arms and for use during surgery were based on clinical practice guidelines for patients with severe haemophilia[9, 10,13].

## Efficacy

## Studies providing efficacy data

Only one of the submitted studies (998HB102, also known as the B-LONG study) contained efficacy data.

This study was an open-label, Phase III trial, with 4 arms, conducted in PTPs aged 12 years and older. The primary objectives of the study were:

· To evaluate the safety and tolerability of rFIXFc;

· To evaluate the efficacy of rFIXFc in all treatment arms;

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[13] Wiedel J, Stabler S, Geraghty S, et al. Joint replacement surgery in hemophilia. *Treatment of Hemophilia*. June 2010;50:1-12.

- To evaluate the effectiveness of prophylaxis over on-demand (episodic) therapy by comparing the annualized number of bleeding episodes between subjects receiving FIXFc on each prevention (prophylaxis) regimen (Arm 1 and Arm 2) and subjects receiving FIXFc on an episodic regimen (Arm 3).

Details of this study are provided in Attachment 2 of this AusPAR.

**Evaluator's conclusions on efficacy**

The PK data generated in the Phase III study demonstrate that the administration of rFIXFc restores plasma FIX activity levels in subjects with FIX deficiency. The degree to which FIX activity is restored (as measured by $C_{max}$ and incremental recovery) is comparable to that achieved with the registered recombinant FIX product BeneFIX when the two products are administered at the same dose. The half-life and AUC of rFIXFc were approximately double those observed with BeneFIX. It would therefore be reasonable to expect that rFIXFc should have comparable clinical efficacy to BeneFIX and that a longer dosage interval should be possible.

The data from the pivotal study establish that rFIXFc is effective in the treatment of bleeding episodes. Subjects rated the response to rFIXFc treatment as 'excellent' or 'good' on 82.0% of occasions. Physicians rated responses as 'excellent' or 'effective' on 98.8% of occasions. A total of 90.4% of bleeding episodes resolved after a single injection of rFIXFc. The dosages used for the treatment of bleeding episodes in the study are considered appropriate.

The study also established that use of a prophylaxis regimen was superior to use of an on-demand or episodic regimen. The two prophylaxis regimens tested resulted in reductions in annual bleeding rate of 83% and 87%, respectively. The two dosage regimens supported by the study[14] are:

- A starting regimen using a fixed once weekly interval with a starting dose of 50 IU/kg and subsequent adjustment of the dose.

- A starting regimen using a fixed dose of 100 IU/kg with an initial dosing interval of 10 days and subsequent adjustment of the dosing interval. The maximum dosing interval should be no more than 14 days.

The study also established efficacy of the product when used in the surgical prophylaxis setting, with response rated as 'excellent' or 'good' in 100% of major surgeries, and modest blood loss.

The submitted data generally meet the requirements laid down by the relevant EMA guidelines[15,16,17].

Overall it is concluded that the efficacy of product has been satisfactorily established for use in PTPs aged 12 years or older.

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[14] See approved PI for finally approved dosage regimen, which recommends starting regimens of either 50 IU/kg once weekly or 100 IU/kg once every 10 days. Either regimen may be adjusted based on patient response.

[15] European Medicines Agency. Points to Consider on Application with 1. Meta-Analyses; 2. One Pivotal Study (CPMP/EWP/2330/99); 2001.

[16] European Medicines Agency. Note for Guidance on the Clinical Investigation of Recombinant Factor VIII and IX Products (CPMP/BPWG/1561/99); 2000.

[17] European Medicines Agency. Guideline on clinical investigation of recombinant and human plasma-derived factor IX products (EMA/CHMP/BPWP/144552/2009); 2011.

**Safety**

**Studies providing evaluable safety data**

The following studies provided evaluable safety data:

· Pivotal Phase III study (998HB102)

The following safety data were collected: general adverse events (AEs), vital signs, laboratory tests (haematology, biochemistry, total IgG and IgG1, IgG2 IgG3, IgG4, coagulation parameters), Nijmegen modified Bethesda assay for inhibitors, and an assay for anti-FIXFc antibodies. Urinalysis and ECG monitoring were not performed.

· Clinical pharmacology study (SYN-FIXFc-07-001)

Study SYN-FIXFc-07-001 was the first-in-man dose escalation study, which examined safety and PK of rFIXFc. Subjects only received single doses of rFIXFc, over the dose range 1 IU/kg to 100 IU/kg and were monitored daily after the infusion up to Day 11 and had a final study visit on Day 30.

· Other studies

The submission included brief reports from two ongoing studies:

· Study 9HB02PED. This is an open label multicentre study of the PK, efficacy and safety of rFIXFc in paediatric (age < 12) PTPs. The cut off date for data to be included in the report was 15 October 2012 and the report itself was dated 12 December 2012. By the cut off date 12 subjects had been enrolled but only 4 subjects had received at least one dose of rFIXFc. The submitted report was brief (11 pages) and provided information on serious AEs (SAEs) and AEs of special interest only.

· Study 9HB01EXT. This is an open label extension study for subjects previously enrolled in either the pivotal Phase III study (998HB102) or the paediatric study (9HB02PED). It is an open label multicentre study of the long term efficacy and safety of rFIXFc. The cut off date for data to be included in the report was 9 October 2012 and the report itself was dated 12 December 2012. By the cut off date 87 subjects from the Phase III study had been enrolled and all had received at least one dose of rFIXFc. No subjects from the paediatric study had been enrolled. The submitted report was brief (12 pages) and provided information on SAEs and AEs of special interest only.

### *Pivotal studies that assessed safety as a primary outcome*

There were no pivotal studies that assessed safety as a primary outcome[18].

**Patient exposure**

In the studies included in the submission, a total of 141 separate subjects[19] received at least one dose of rFIXFc as summarised in the following table.

**Table 3: Exposure to rFIXFc in clinical studies**

| Study | Number of subjects |
| --- | --- |
| Study 998HB102 | 123 |

[18] Sponsor clarification: A primary objective of Study 998HB102 was "to evaluate the safety and tolerability of rFIXFc".

[19] Sponsor clarification: These subjects were not necessarily unique as there is a possibility of overlap of subjects from Phase I/IIa to Phase III. The sponsor suggested the total included more than 130 unique subjects exposed to rFIXFc.

| Study | Number of subjects |
|---|---|
| Study SYN-FIXFc-07-001 | 14 |
| Study 9HB02PED | 4 |
| Total | 141[19] |

**Evaluator comment:** A total of 87 subjects from 998HB102 continued into the extension study 9HB01EXT and are not included in the table as they are not separate individuals. Subjects in SYN-FIXFc-07-001 received only one dose of rFIXFc and the only data provided for the 4 subjects from 9HB02PED related to SAEs and AEs of special interest. Therefore assessment of the safety of rFIXFc relies almost entirely on the data generated in study 998HB102.

The most recent EMA guideline on FIX products[20] states that: 'The number of patients typically needed to be enrolled into the preauthorisation clinical trials is 40.'

The extent of exposure in Study 998HB102 in terms of the number of weeks on rFIXFc is summarised in Table 4.

**Table 4: Study 998HB102: Extent of exposure by number of weeks on rFIXFc**



A total of 115 subjects were on rFIXFc for at least 26 weeks, and 56 subjects for at least 52 weeks. The extent of exposure in terms of exposure days and number of injections is summarised in Table 5.

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[20] European Medicines Agency. Guideline on clinical investigation of recombinant and human plasma-derived factor IX products (EMA/CHMP/BPWP/144552/2009); 2011.

**Table 5: Study 998HB102: Extent of exposure by number of exposure days and number of injections**



The median number of exposure days was 49.0 and the median number of injections was 50.0.

## Safety issues with the potential for major regulatory impact

### Liver toxicity

Liver function testing did not suggest any evidence of drug-induced hepatotoxicity.

### Haematological toxicity

Haematology testing did not suggest any evidence of drug induced haematological toxicity.

### Serious skin reactions

There were no serious AEs involving the skin reported.

### Cardiovascular safety

One subject developed an SAE of worsening of angina pectoris during the trial. He had a prior history of ischaemic heart disease including angina pectoris and myocardial infarction. There were no other notable cardiovascular events.

### Unwanted immunological events

There were no SAEs related to the immune system.

## Post marketing data

As the product had not been approved for marketing in any jurisdiction at the time of this submission, the submission did not include any post marketing data.

**Evaluator's conclusions on safety**

The overall safety database included a total of 141 subjects[21], which is well in excess of the number required by the most recent EMA guideline. The extent of safety testing is therefore considered acceptable.

Known safety issues associated with FIX replacement therapy products include development of inhibitors, thrombotic events and allergic and anaphylactic reactions.

The submitted data for Alprolix were essentially limited to previously treated patients aged 12 or over, with no prior history of inhibitors. There were no reports of inhibitors or serious allergic reactions suggesting that the incidence of these adverse effects is acceptably low, in this population. The submitted data also suggest that the product is not associated with significant thrombotic AEs.

The only treatment related AEs that occurred in more than one patient were oral paraesthesia and headache. Neither of these was considered serious. Monitoring of biochemistry, haematology and coagulation parameters and vital signs did not suggest any unexpected toxicities.

## First round benefit-risk assessment

**First round assessment of benefits**

The benefits of rFIXFc in the proposed indication are:

· Efficacy in the control of bleeding episodes;

· Efficacy in the prevention of bleeding episodes when administered as routine prophylaxis;

· Efficacy in the management of bleeding associated with surgical procedures;

· A reduced frequency of dosing when compared to currently available FIX replacement products;

· A decreased risk of viral transmission compared to plasma derived FIX.

**First round assessment of risks**

The risks of rFIXFc in the proposed indication are:

· A possible risk of inhibitor development, vascular thrombotic events and allergic reactions. The available data suggest that the incidence of these effects in the proposed population is acceptably low.

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

The benefit-risk balance of rFIXFc, in previously treated subjects aged 12 years or over, is considered favourable. The submitted data support use for episodic (on-demand) therapy, routine prophylaxis and surgical prophylaxis when the product is given by bolus infusion.

The current data do not support use of the product:

· in children aged less 12 years;

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[21] Sponsor clarification: These subjects were not necessarily unique as there is a possibility of overlap of subjects from Phase I/IIa to Phase III. The sponsor suggested the total included more than 130 unique subjects exposed to rFIXFc.

· in previously untreated patients;

· by continuous infusion in surgery;

· for immune tolerance induction (ITI) in patients with FIX inhibitors.

The sponsor is not seeking approval for use in these situations at the current time.

### First round Recommendation regarding authorisation

It is recommended that the application for registration be approved.

The clinical evaluator's recommended revisions to clinical aspects of the draft PI are beyond the scope of the AusPAR.

## Clinical questions

### General

Please provide an assurance that the lyophilised product proposed for registration in Australia is identical to that used in the pivotal Phase III study (with respect to formulation and manufacturing processes).

### Safety

One subject in Study 998HB102 developed clinically significant elevations of creatinine and urea: urea was elevated at screening (10.7 mmol/L), normal at baseline and elevated at Week 26 (15.7) and Week 52 (16.1). Creatinine was at a borderline level at screening (118 µmol/L), normal at baseline and elevated at Week 26 (255) and Week 52 (158). It is noted that the subject had a number of medical conditions at baseline including morbid obesity, Type II diabetes, hypertension, high cholesterol and bipedal oedema. The development of renal impairment in this subject does not appear to have been reported as an AE and the study report does not comment on the case. Is the sponsor able to provide any further information or comment in relation to this subject to exclude a nephrotoxic effect of rFIXFc?[22]

## Second round evaluation of clinical data submitted in response to questions

The sponsor's responses to the clinical questions (above) are taken into account in the Delegate's overview (see *Overall conclusion and risk/benefit assessment*, below). Therefore a second round evaluation report was not prepared.

### Second round benefit-risk assessment

Not applicable.

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[22] The sponsor provided information about this subject in the response to a TGA request for further information, and concluded that a nephrotoxic effect of rFIXFc treatment is unlikely based on chemistry data from non-clinical toxicology studies and the Phase III study, and further review of data for this subject demonstrating multiple factors potentially contributing to his renal insufficiency.

# V. Pharmacovigilance findings

**Risk management plan**

The sponsor submitted a Risk Management Plan (RMP), Alprolix Aus-RMP version 1 (data lock point 15 October 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 6.

**Table 6: Summary of ongoing safety concerns**

| Risk | Planned actions(s) |
|---|---|
| Important identified risks | None |
| Important potential risks | Inhibitor development |
| | An inhibitor is defined as a neutralizing antibody value ≥ 0.6 BU/mL by Nijmegen-modified Bethesda assay and confirmed on retesting within 2 to 4 weeks. |
| | Allergic reaction or anaphylaxis |
| | A serious allergic reaction associated with administration of rFIXFc is defined as an event that is ≥ Grade 2 on the Recommendations for Grading of Acute and Subacute Toxic Effects on the WHO scale. |
| | Thrombotic events |
| | A thrombotic event in association with the administration of rFIXFc is defined as any event suggestive of a vascular thrombotic event with the exception of IV injection thrombophlebitis. |
| Important missing information | Safety profile in patients ≥ 65 years old |
| | Safety profile in children < 12 years old |

OPR evaluator comment: Notwithstanding the evaluation of the non-clinical and clinical aspects of the safety specifications, the summary of ongoing safety concerns appear to be consistent with that included in the proposed PI.

**Pharmacovigilance plan**

The following is a summary of pharmacovigilance activities proposed in the Aus-RMP:

**Table 7: Pharmacovigilance activities proposed by the sponsor**

| Safety concern | Planned action(s) |
|---|---|
| Important identified risks | N/A |

| Safety concern | Planned action(s) |
|---|---|
| **Important potential risks** | |
| Inhibitor development:<br><br>An inhibitor is defined as a neutralizing antibody value ≥ 0.6 BU/mL by Nijmegen modified Bethesda assay and confirmed on retesting within 2 to 4 weeks | Routine pharmacovigilance activities:<br><br>· Cumulative analyses in Periodic Safety Update Reports (PSURs).<br>· Pediatric study 9HB02PED.<br>· Safety extension study 9HB01EXT.<br><br>Additional pharmacovigilance activities:<br><br>· Expedited reporting to regulators of an inhibitor.<br>· Targeted follow-up by questionnaire of an inhibitor from spontaneous reports, other programs where data are being handled as solicited, and all clinical trial SAEs. |
| Allergic reactions or anaphylaxis<br><br>A serious allergic reaction associated with administration of rFIXFc is defined as an event that is ≥ Grade 2 on the Recommendations for Grading of Acute and Subacute Toxic Effects on the WHO scale | Routine pharmacovigilance activities:<br><br>· Cumulative analyses in PSURs.<br>· Pediatric study 9HB02PED.<br>· Safety extension study 9HB01EXT.<br><br>Enhanced pharmacovigilance activities:<br><br>· Expedited reporting to regulators of a serious allergic reaction or anaphylaxis.<br>· Targeted follow-up by questionnaire of a serious allergic reaction or anaphylaxis from spontaneous reports, other programs where data are being handled as solicited, and all clinical trial SAEs. |
| Thrombotic events<br><br>A thrombotic event in association with the administration of rFIXFc is defined as any event suggestive of a vascular thrombotic event with the exception of IV injection thrombophlebitis | Routine pharmacovigilance activities:<br><br>· Cumulative analyses in PSURs.<br>· Pediatric study 9HB02PED.<br>· Safety extension study 9HB01EXT.<br><br>Enhanced pharmacovigilance activities:<br><br>· Expedited reporting to regulators of serious thrombotic events.<br>· Targeted follow-up by questionnaire of serious thrombotic events from spontaneous reports, and other programs where data are being handled as solicited, and all clinical trial SAEs. |

| Safety concern | Planned action(s) |
|---|---|
| **Important missing information** | |
| Safety profile in patients aged ≥ 65 years old | Routine pharmacovigilance activities:<br><br>· Cumulative analyses in PSURs.<br><br>· Limited data from safety extension study 9HB01EXT. |
| Safety profile in children < 12 years old | Routine pharmacovigilance activities:<br><br>· Cumulative analyses in PSURs.<br><br>· Pediatric study 9HB02PED.<br><br>· Potentially limited data from safety extension study 9HB01EXT. |

**Risk minimisation activities**

The sponsor has stated: 'Because the most important risks of rFIXFc 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.'

**Risk minimisation plan**

Routine risk minimisation is proposed for all the safety concerns.

**Reconciliation of issues outlined in the RMP report**

The following provides the OPR evaluator's recommendations in the first round evaluation report, a summary of the sponsor's responses to these recommendations, and the OPR evaluator's evaluation of the sponsor's responses.

*Recommendation 1*

Safety considerations may be raised by the nonclinical and clinical evaluators through the TGA consolidated request for further information or the nonclinical and clinical evaluation reports respectively. It is important to ensure that the information provided in response to these includes a consideration of the relevance for the RMP, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, the sponsor should provide information that is relevant and necessary to address the issue in the RMP.

The sponsor acknowledged this statement and confirmed that consideration has been given to comments from other TGA sources.

OPR evaluator comment: The sponsor's response is satisfactory.

*Recommendation 2*

It should be noted that clinical studies are considered 'additional pharmacovigilance activities' whilst reporting of findings and AEs in the PSURs are considered 'routine pharmacovigilance'.

The sponsor acknowledged this statement and agreed to modify relevant tables in the RMP accordingly.

OPR evaluator comment: The sponsor's response is satisfactory.

### *Recommendation 3*

The sponsor should provide an attachment to the RMP setting out all the forthcoming studies and the anticipated dates for their submission in Australia.

Sponsor's response (in part): 'Should the Delegate request an attachment to the RMP as recommended by the evaluator, Biogen Idec agrees to provide such an attachment setting out a forthcoming study and the anticipated date for its submission in Australia.'

OPR evaluator comment: It is recommended that the Delegate requests the sponsor to submit an attachment to the Aus-RMP setting out all the forthcoming studies and the anticipated dates for their submission in Australia. This will ensure key milestones of post-marketing pharmacovigilance and risk minimisation activities are clearly identified and monitored.

In addition, 'use in previously untreated patients' should be added to the safety concern list under 'Missing Information'. The planned study to evaluate the safety and efficacy of rFIXFc in previously untreated patients should be added as an additional pharmacovigilance activity.

### *Recommendation 4*

It is expected that updates and findings of the ongoing studies will be communicated to the TGA and included in PSURs when available. It is recommended that results of these studies are communicated to the TGA at the same time as they are communicated to other regulatory agencies.

Sponsor's response: 'Biogen Idec will continually assess the emerging data obtained from ongoing studies within the pharmacovigilance plan as well as from spontaneous and other sources. The data collected via the described pharmacovigilance plan will inform any required updates to risk minimization measures. Results of these studies will be communicated to regulatory agencies, including TGA in clinical study reports. PSURs will include relevant analyses and will be submitted according to the local regulations. Important potential risks will be reported in an expedited manner to regulators as outlined in the RMP.'

OPR evaluator comment: The sponsor's response is satisfactory.

### *Recommendation 5*

It is recommended that the Australian Bleeding Disorders Registry be used to monitor patients who receive Alprolix. Relevant findings from the Registry should be reported in the Periodic Safety Update Reports (PSURs) and communicated to the TGA.

Sponsor's response: 'Biogen Idec acknowledges the recommendation to use the Australian Bleeding Disorders Registry to monitor patients who receive Alprolix and will contact the Registry to obtain additional information required to assess the feasibility of implementing this recommendation.'

OPR evaluator comment: The sponsor's response is satisfactory.

### *Recommendation 6*

In determining the appropriate risk minimisation measures, each safety concern needs to be individually considered and the selection of the most suitable risk minimisation measures should take into account the seriousness of the potential adverse reaction(s) and its severity, its preventability or the clinical actions required to mitigate the risk, the indication, the route of administration, the target population and the healthcare setting for the use of the product. The sponsor should therefore

provide justification to why routine risk minimisation will be sufficient to reduce the risks described in the safety specification.

Sponsor's response: 'As noted in the RMP, rFIXFc was well tolerated in clinical development and the AE profile was generally consistent with that expected of the haemophilia B population. There were no cases of inhibitor formation, anaphylaxis or vascular thrombosis. Because the most important risks of rFIXFc treatment remain potential risks rather than known risks, it is proposed that the potential risks can be appropriately managed and minimized by guidance in the Product Information without a requirement for any enhanced risk minimization. Information from all sources will continuously be assessed and appropriate changes to risk minimization measures, including labelling documents, will be undertaken as needed.'

OPR evaluator comment: The sponsor's response is satisfactory.

### Recommendation 7

As the product is expected to be self-administered IV by a proportion of patients, there is an increased risk of inappropriate preparation, administration and storage of the product at home which can have potentially severe consequences. The sponsor should undertake to provide additional educational material and periodic training to patients and their carers on important points regarding the correct indication, preparation, storage and administration of the product.

Sponsor's response (in part): 'Biogen Idec acknowledges that appropriate materials and training will be required in order to ensure appropriate preparation, administration and storage of the product for those patients and carers who choose to self-administer Alprolix'.

OPR evaluator comment: The sponsor's response is satisfactory. The sponsor should add the additional educational materials including the Directions for Use, infusion training kits, and patient pack in the RMP as additional risk minimisation activities.

Printed educational materials for healthcare providers and patients/carers that have not been previously provided to the TGA should be submitted for review before they are supplied.

### Recommendations 8, 9 and 10

These related to recommended amendments to statements in the PI (and consequently, to the Consumer Medicine Information) with the aim to strengthen routine risk minimisation activities. Details of these recommendations, the sponsor's responses and follow-up recommendations from the OPR evaluator are beyond the scope of the AusPAR.

## Advice from the Advisory Committee on the Safety of Medicines

This application was submitted for advice from the March 2014 meeting of the Advisory Committee on the Safety of Medicines (ACSOM).

## Summary of recommendations to the delegate

It is considered that the sponsor's response to the OPR evaluator's recommendations (above) has adequately addressed most of the issues identified in the RMP evaluation report. Outstanding issues are identified above.

### Suggested wording for conditions of registration

Implement Aus-RMP version 1 (data lock point 15 October 2012) and any future updates as a condition of registration.

# VI. Overall conclusion and risk/benefit assessment

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

## Quality

There was no objection to registration. Conditions of registration were recommended, regarding batch release conditions.

Measured functional characteristics of rFIXFc were consistent with expected FIX and Fc functionalities. There was no indication from characterisation of biological activity that Fc fusion impeded FIX functionality.

## Nonclinical

There was no objection to registration. Evidence was shown that FcRn KO mice had comparable elimination half-lives for rFIXFc and BeneFIX, supporting the proposed basis for the long half-life observed for Alprolix.

## Clinical

### Overview of data

The pivotal study was called 998HB102 or "B-LONG"; a report has been published[23]. The study was a Phase III study of PK, efficacy and safety in 123 subjects with severe haemophilia B. Subjects were PTPs aged ≥12 years. In a subgroup, PK comparisons were made with BeneFIX.

There was also a first-in-human, Phase I/IIa study called "SYN-FIXFc-07-001" in 14 subjects. Escalating single doses were studied.

There was a population PK study drawing on results from the above two studies.

There were safety reports from the ongoing studies 9HB02PED and 9HB01EXT. Study 9HB02PED is a trial in PTPs aged < 12 years (planned enrolment approximately 20; completion approximately June 2015). Study 9HB01EXT is an extension study for subjects previously enrolled in either 99HB102 or the paediatric study.

In the pivotal study, 117/123 subjects exclusively used the lyophilised formulation made using a 15000 L bioreactor. The lyophilised product proposed for registration is essentially the same as that predominantly used in the Phase III study.

### Pharmacokinetics

Incremental recovery (IR) was 0.92 IU/dL for every 1.0 IU/kg given, similar to the result for BeneFIX (0.95) in the same study. The evaluator drew attention to the high IR for BeneFIX relative to results from earlier studies, and raised the possibility that rFIXFc may, like BeneFIX, have a lower IR than plasma derived FIX.

No other PK concerns were noted by the clinical evaluator.

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[23] Powell et al. Phase III study of recombinant Factor IX Fc Fusion protein in haemophilia B. *NEJM* 2013;369: 2313-2323.

The half-life in terms of FIX activity was measured as 82.1 h (see discussion in Powell et al 2013, page 2319). The 'time to 3% FIX activity' is longer for Alprolix than for BeneFIX (5.7 days versus 2.8 days).

Also relevant given that albumin and IgG may be handled by the same FcRn mechanism as Alprolix, the population PK analysis drawing on the Phase I/IIa and Phase III studies included (amongst other variables) IgG1 concentration and albumin concentration but found body weight to be the only covariate significantly affecting PK.

**Efficacy**

*Choice of dose regimen*

Dose regimen in B-LONG was chosen on the basis of results from the Phase I/IIa single dose study SYN-FIXFc-07-001 (at 50 IU/kg, over 70% of the population would have FIX activity of 1% above baseline on Day 7).

*Pivotal study: Study 998HB102 ("B-LONG")*

This was an open label study across 17 countries (including Australia), conducted from 2010 to 2012. Those studied were previously treated patients with severe haemophilia B (endogenous FIX ≤ 2% of normal levels) aged 12 years and older (inclusion and exclusion criteria are detailed in the CER (Attachment 2). There were four treatment arms, summarised below:

1. 50 IU/kg initial dose then PK assessment to individualise dose for a prophylaxis regime at a fixed 7 day interval (a subgroup was used in a sequential, non-randomised PK comparison of Alprolix and BeneFIX, and to compare Alprolix at initial and 26 week timepoints).

2. 100 IU/kg initial dose then PK assessment to individualise dose interval (initially set at 10 days) for a prophylaxis regime using a fixed 100 IU/kg dose.

3. 50 IU/kg initial dose then PK assessment to determine dose to be used for an on-demand regimen.

4. Subjects scheduled for surgery. 50 IU/kg initial dose then PK assessment and treatment with 40-100 IU/kg for perioperative management.

Subjects were not randomised into these arms; rather, they were assigned an arm based on "standard of care and investigator decision, following discussion with each subject". Most patients self-administered Alprolix, at home.

123 males were enrolled, a reasonable number given the rarity of the disease but also the requirement for sufficient clinical data noting the novel design of eftrenonacog alfa:

· Arm 1 (prophylaxis, weekly, dose-adjusted) had 63 subjects.

· Arm 2 (prophylaxis, interval-adjusted, 100 IU/kg) had 29 subjects.

· Arm 3 (on-demand) had 27 subjects.

· Arm 4 (peri-operative) had 4 subjects (though 12 participated in this Arm in total, that is, 8 came across from other arms).

All subjects had severe haemophilia B (baseline FIX levels < 2%, mostly < 1%). Prior to enrolment, 60% had received episodic dosing, 40% prophylactic. 11 subjects were 12 to 17 years of age (two were 12 years of age, two were 14 years, three were 15 years, one was 16 years, three were 17 years); the median age was 30 years.

The primary efficacy endpoint was the annualised bleeding rate (ABR) in the 'efficacy period' (see Attachment 2, CER, for definition of ABR). Annualised bleeding rate (negative binomial model) was 3.12 in Arm 1 (prophylaxis, 7 day interval), 2.40 in Arm 2

(prophylaxis, 100 IU/kg), and 18.67 in Arm 3 (on-demand). There was no real change in bleeding rate from pre-study once the population had been stratified by prior use of prophylactic versus on-demand therapy. The pattern of dosage adjustment in Arm 1 supports a starting dose of 50 IU/kg then change of dose based on PK or clinical need. The pattern of dose interval adjustment in Arm 2 supports initial use at 100 IU/kg every 10 days, and a maximum interval of 14 days.

The sponsor's pharmacokinetics/pharmacodynamics analysis suggests that in the prophylaxis setting bleeding was less likely with FIX activity > 10%. This supports the evaluator's view about dose regimen. Modelling suggests that the 14 day interval for 100 IU/kg dosing be used only after PK based dose regimen individualisation (that is, not at the outset) and that an interval > 14 days should not be used.

There were 14 major surgical procedures in 12 subjects in Arm 4: mainly orthopaedic, with no or few major abdominal operations though one patient underwent repair of a large abdominal fistula (and needed packed cells and FFP due to diffuse oozing from the wound). Responses for major procedures were rated as excellent (13/14) or good (1/14).

### Safety

Most data were from pivotal study 998HB102. In that study, 113 subjects received Alprolix for 26 or more weeks, and 56 for at least 1 year.

The clinical evaluator drew attention to the report of hypertension in 6 subjects in the pivotal study (5.0%), aged 33 to 56 years, with 2/6 having a prior history of hypertension. Treatment was required in 3 subjects. Blood pressure (BP) was also increased in one subject given < 50 IU/kg and in one subject given 50 IU/kg in the Phase I/IIa study. However, BP monitoring revealed a more pronounced signal for low BP than for high BP. A cross-sectional study cited by the sponsor[24] claims an increased prevalence of hypertension in haemophilia (mostly haemophilia A).

There were no AEs suggestive of serious allergic reactions or vascular thrombosis.

One subject developed elevated creatinine and urea but that subject had co-morbidities including Type II diabetes and hypertension, and used (amongst other medications) celecoxib and furosemide. No other subjects in B-LONG had elevated urea and creatinine. In the Delegate's view, this product is unlikely to be nephrotoxic.

There was no evidence of inhibitor development. The evaluator notes the studied population would be at low risk of inhibitor development, so any difference between Alprolix and existing FIX products in risk of inhibitor development may not be inferred from this study.

### Clinical evaluator's recommendation

The clinical evaluator recommended the application be approved.

### Risk management plan

The RMP proposed by the sponsor was considered generally acceptable by the TGA's OPR. The following condition of registration is recommended:

· Implement Aus-RMP version 1 (data lock point 15 October 2012) and any future updates as a condition of registration.

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[24] Van de Putte et al. Increased prevalence of hypertension in haemophilia patients. *Thromb Haemost*. 2012;108:750-755.

In response to this overview, the Delegate requested the sponsor provide an attachment to the RMP setting out all the forthcoming studies and the anticipated dates for their submission in Australia.

## Risk-benefit analysis

### Delegate's considerations

#### *Pharmacology*

In the response to this overview, the sponsor should address whether there are known polymorphisms of the gene expressing FcRn that may predictably affect FcFIX half-life[25].

#### *Efficacy*

The lack of randomisation (especially for Arms 1 to 3) makes any formal comparisons of efficacy across arms problematic, but the better outcomes in prophylactic arms relative to on-demand arms recur in other studies of FIX replacement in haemophilia B. It is not possible to state that Arm 1's approach (that is, weekly, dose adjusted) is better than Arm 2's (interval adjusted, 100 IU/kg) because a large difference in mean ABR was not seen, and subjects were not randomised into the arms so confounding factors are likely to exist (and there was only fair balance of measured baseline characteristics such as age, across these arms).

Regarding dosage at a fixed dose of 100 IU/kg, the evaluator recommended the dosing interval not exceed 14 days. The Delegate supports the evaluator's view that the experience is too limited to recommend dosing intervals > 14 days. In addition, although the sponsor points to the fraction of patients with, for example, a dosing interval of 14 or more days 'in the last 3 months of the study', the ABRs discussed above refer to the 'efficacy period' (not just the last 3 months). The Delegate proposed to seek ACPM advice on whether this view is supported by the committee or whether it consider that dosing intervals > 14 days might be recommended in the PI since the dose regimen is to be 'individualised' on the basis of PK assessment.

#### *Safety*

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

Tangentially, the sponsor's website claims that interim paediatric data show a prolonged half-life of Alprolix in children; however no data have been reviewed here[26].

#### *Overall risk-benefit*

Benefit-risk is favourable in the studied population. The product has the advantage of requiring less frequent dosing (but whether the fixed dose or fixed interval approach is better is unclear). Less frequent dosing is particularly significant in the prophylactic setting and access to this product may encourage more patients to adopt prophylaxis.

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[25] The Sponsor provided further information in the Pre-ACPM response: The neonatal Fc receptor (FcRn) is encoded by FCGRT. Known polymorphisms of the FCGRT gene do not appear to affect half-life of IgGs and presumably Fc-containing proteins.
[26] Sponsor comment: this data was not available at the time of submission and so could not be included in the dossier.

## Summary of issues

Alprolix is a FIX molecule covalently attached to the dimeric Fc domain of human IgG1. It has a prolonged half-life, by virtue of this Fc component. This allows a longer dosing interval, seemingly without any impact on efficacy or safety but completed trials have been limited to previously treated patients 12 years of age or older and there is no experience in treatment naïve subjects and no meaningful efficacy or safety information in the paediatric population. Inhibitor formation has not been observed but the population studied to date has an intrinsically lower risk of inhibitor formation.

## Proposed action

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

The Delegate's proposed revisions to the PI, and details of PI related requests for information from the sponsor, are beyond the scope of the AusPAR.

## Request for ACPM advice

The Delegate proposed to seek general advice on this application from the ACPM and in addition to request the committee provide advice on the following specific issues:

1.  In what haemophilia B population if any does Alprolix have a positive benefit-risk balance?

If a population with positive benefit-risk balance can be defined, then:

2.  Is evidence sufficient to support dosing using the 100 IU/kg dose at intervals > 14 days?

The committee was also requested to provide advice on any other issues that may be relevant to:

·   a decision on whether or not to approve this application (including conditions of registration).

·   negotiation of an acceptable Product Information document.

## Response from sponsor

### Topic 1: In the Delegate's overview, ACPM's advice is being sought on the following questions:

·   In what haemophilia B population if any does Alprolix have a positive benefit-risk balance?

·   If a population with positive benefit-risk balance can be defined, then is evidence sufficient to support dosing using the 100 IU/kg dose at intervals > 14 days?

Similarly, the Delegate proposes to ask ACPM whether they support the view that the dosing interval not exceed 14 days or consider that dosing intervals > 14 days might be recommended in the PI since the dose regimen is to be individualised on the basis of PK assessment.

Sponsor response:

Alprolix represents an important therapeutic innovation as the first potential therapy for haemophilia B with a modification that enables the prolongation of circulating half-life while preserving full clinical activity as demonstrated by the Phase III study (998HB102) results.

The Phase III study enrolled 123 PTPs ≥ 12 years of age with severe haemophilia B. The subjects were representative in terms of race, geographic location, and disease co-morbidities. The study included 11 subjects 12 to 17 years of age, allowing evaluation of Alprolix in this adolescent group.

Alprolix showed a significantly improved elimination half-life (2.43 fold longer) in a subgroup of 22 subjects compared to BeneFIX; the prolongation of half-life of Alprolix was also observed in all other study subjects. There was sufficient exposure to allow for an adequate evaluation of ABR and inhibitor incidence. Alprolix was generally well tolerated with an acceptable safety profile across all subgroups studies. No inhibitor was detected in any subject exposed to Alprolix and no anaphylactic, serious hypersensitivity, or vascular thrombotic events were reported. Efficacy was demonstrated for the treatment of episodic bleeding as well as for routine prophylaxis and perioperative management. In all subgroups studied, including in subjects 12 to 18 years of age, efficacy was consistent with the overall group. All subjects in the sequential PK group had a prolongation of half-life compared to Benefix. Both a weekly dosing regimen and an individualized interval regimen were associated with a significant reduction in ABR (> 80%) compared to episodic (on-demand) treatment.

The clinical development program for Alprolix used a stepwise approach to gain experience with Alprolix in previously treated patients 12 years of age and older prior to investigating Alprolix in younger subjects. As noted in response to Topic 5 (below), Biogen Idec plans to submit a post approval variation to the TGA for Alprolix, including data from the ongoing paediatric study (9HB02PED), as well as revised draft labelling in order to amend the Alprolix indication to include patients < 12 years of age. As also noted in response to Topic 3 (below), a study (998HB303) is currently planned to evaluate safety and efficacy in previously untreated patients (PUPs) with severe haemophilia B.

The overall benefit-risk profile of Alprolix is positive for the treatment of individuals with haemophilia B. This positive benefit-risk profile was consistent across all subgroups studied. As a generally well tolerated, long acting replacement factor, Alprolix offers the potential to improve acceptance of prophylactic treatment and offers sustained protection in the setting of prophylaxis and efficacy in the setting of control of bleeding and perioperative management. Reducing the frequency of treatment is expected to confer public health benefits in terms of compliance and improved long term outcomes in patients with haemophilia B. The population evaluated in the Phase III study results is representative of the general population of adults and adolescents ≥ 12 years of age with haemophilia B, which is the population proposed in the draft labelling. Further support for the proposed dosing guidance specific to the subset of patients who may benefit from dosing intervals > 14 days is provided in Response to Topic 7.

***Topic 2: In the Delegate's overview, it was noted that blood pressure monitoring revealed a more pronounced signal for low blood pressure than for high.***

Sponsor response:

In the Phase III study (998HB102), abnormal low BP was pre-defined as follows:

·    Systolic BP < 90 mmHg or > 30 mmHg decrease from baseline.

·    Diastolic BP < 50 mmHg or > 20 mmHg decrease from baseline.

Of the 114 subjects in the Phase III study with vital signs evaluated (with a baseline assessment and at least 1 post-baseline assessment) in Arms 1, 2, and 3 combined, there were 5 subjects (4.4%) with an abnormal low systolic BP assessment; and 9 subjects (7.9%) with an abnormal low diastolic BP assessment, including 3 subjects with abnormal low systolic and diastolic BP values. These 11 unique subjects were between 12 to 56 years of age (mean 31 years). Blood pressure abnormalities were generally mild, transient,

and none were associated with an AE suggestive of hypotension, hypersensitivity or anaphylaxis. All 11 subjects completed the Phase III study.

Overall, there was no pattern or consistent trend in abnormal decrease in BP observed in the Phase III study. The data do not suggest an association of hypotension with Alprolix.

***Topic 3: In the Delegate's overview, it was noted that the sponsor should provide an attachment to the RMP setting out all the forthcoming studies and the anticipated dates for their submission in Australia.***

Sponsor response:

Biogen Idec agrees to provide such an attachment setting out a forthcoming study and the anticipated date for its submission in Australia. An open label, multicentre study (998HB303) is currently planned to evaluate the safety and efficacy of Alprolix in the prevention and treatment of bleeding in previously untreated patients (PUPs) with severe haemophilia B. The study will end when 40 PUPs reach 100 EDs with Alprolix. It is estimated that the first subject will be consented in late 2014 and that the study duration will be approximately 8 years.

***Topic 4: In the Delegate's overview, it was noted that the sponsor should address in [this] response whether there are known polymorphisms of the gene expressing FcRn that may predictably affect FcFIX half-life.***

Sponsor response:

The FcRn is encoded by FCGRT, a 14 kb gene. Few data are available on the potential polymorphisms of FCGRT. A variable number tandem repeat (VNTR) located in the promoter of FCGRT has been described and its impact on monoclonal antibodies (mAb) PK was studied[27]. No effects were seen of VNTR genotype on elimination clearance or distribution volume of the mAb[28]. Furthermore, it was reported that FCGRT is rarely affected by copy number variation (CNV). In the one individual who had 3 copies of FCGRT (all others had 2 copies), the mAb concentrations and PK were no different than those with 2 copies of the gene. In conclusion, known polymorphisms of the FCGRT gene do not appear to affect half-life of IgGs and presumably Fc-containing proteins.

***Topic 5: In the Delegate's overview, it is noted that, 'tangentially, the sponsor's website claims that interim paediatric data show a prolonged half-life of Alprolix in children, however, no data have been reviewed here'.***

Sponsor response:

The original marketing authorisation applications for Alprolix in the United States (US) and Australia included results from the Phase III study (998HB102) demonstrating the safety and efficacy and prolonged PK of Alprolix in subjects 12 years of age and older with haemophilia B.

The US Food and Drug Administration (FDA) accepted Biogen Idec's proposal to provide newly available interim pharmacokinetic (PK) data from the ongoing paediatric study (9HB02PED), as well as revised draft labelling broadening the indication to patients less than 12 years of age, during the initial review of the application. This interim paediatric PK data, which is referenced on Biogen Idec's website, supports the extrapolation of the benefits of Alprolix observed in subjects ≥ 12 years of age to patients < 12 years of age and enables guidance of dosing in these younger paediatric patients.

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[27] Sachs UJH, Socher I, Braeunlich CG et al. A variable number of tandem repeat polymorphism influences the transcriptional activity of the neonatal Fc receptor α-chain promoter. *Immunology*. 2006;119: 83-89.
[28] Passot C, Azzopardi N, Renault S et al. Influence of FCGRT gene polymorphisms on pharmacokinetics of therapeutic antibodies. *mAbs*. 2013;5:4, 614-619.

Biogen Idec plans to submit a post approval variation to the TGA for Alprolix, including data from the ongoing paediatric study (9HB02PED), as well as revised draft labelling in order to amend the Alprolix indication to include patients < 12 years of age.

The remainder of the sponsor's response addressed matters relating to PI revisions 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, considered Alprolix lyophilised powder for injection containing 250, 500, 1000, 2000, 3000 IU of eftrenonacog alfa to have an overall positive benefit-risk profile for the indication;

*Alprolix is a long-acting anti-haemophilic factor (recombinant) indicated in adults and children (>12 years) with haemophilia B (congenital factor IX deficiency) for:*

- *Control and prevention of bleeding episodes;*

- *Routine prophylaxis to prevent or reduce the frequency of bleeding episodes;*

- *Perioperative management (surgical prophylaxis).*

***Proposed conditions of registration:***

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

***Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments:***

The ACPM agreed with the Delegate to the proposed amendments to the PPI and CMI and specifically advised on the inclusion of the following:

- a statement in the *Dosage and Administration* section of the PI and relevant sections of the CMI regarding appropriate directions for use.

- A statement on travel advice in the PI.

- Amendment of the CMI to better reflect Australian circumstances and with reference to the standard CMI template and the Usability Guidelines.

***Specific advice:***

The committee was requested to provide advice on the following specific issue:

- In what haemophilia B population if any does Alprolix have a positive benefit-risk balance?

The ACPM advised that the evidence submitted demonstrated a positive benefit-risk balance in the population delineated in the indication and derived from the clinical trials. The committee noted that although the pivotal study was performed in heavily treatment experienced men and boys with severe haemophilia B the ACPM was of the view that it is likely that Alprolix will be shown to be effective in newly diagnosed patients in the ongoing studies on that topic.

In addition, the ACPM noted that Alprolix will be useful for patients on regular prophylaxis as the prolongation of 'effective' factor IX levels reduces exposure to bleeding risk. For patients using on-demand therapy, there may be benefits from the more prolonged

'effective' factor IX levels as well as a reduction in infusions to treat bleeding episodes. The ACPM also considered that it was reasonable to extend availability of product to children under the age of 12 years as this patient group is included in the extension study (Study 9HB01EXT).

·    If a population with positive benefit-risk balance can be defined, then:

–    Is evidence sufficient to support dosing using the 100 IU/kg dose at intervals > 14 days?

The ACPM noted that in Arm 2 of the pivotal study (Study 99HB102), with dosing based on a target of > 3% of normal factor IX levels, the mean number of days between infusions was 13 with annualised bleeding rates comparable to prior prophylactic therapy. However, the evidence suggests that bleeding episodes were significantly less likely when factor IX levels were > 10%. The ACPM considered that pharmacokinetic data and information on the timing of bleeding episodes in patients in Arm 2 could potentially support extension of dosing beyond 14 days.

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 Alprolix powder for injection, containing eftrenonacog alfa 250 IU, 500 IU, 1000 IU, 2000 IU and 3000 IU and diluent, indicated for:

*Alprolix is a long acting anti-haemophilic factor (recombinant) indicated in adults and children (≥ 12 years) with haemophilia B (congenital factor IX deficiency) for:*

·    *Control and prevention of bleeding episodes;*

·    *Routine prophylaxis to prevent or reduce the frequency of bleeding episodes;*

·    *Perioperative management (surgical prophylaxis)*

**Specific conditions of registration applying to these goods**

·    The ALPROLIX Risk Management Plan, Aus-RMP version 1 (data lock point 15 October 2012) and any future updates, as agreed with the TGA will be implemented in Australia.

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

# Attachment 1. Product Information

The Product Information approved for Alprolix at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

# Attachment 2. Extract from the Clinical Evaluation Report

**Therapeutic Goods Administration**

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au  Phone: 1800 020 653  Fax: 02 6232 8605
**http://www.tga.gov.au**