Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Albutrepenonacog alfa (rch)

Proprietary Product Name: Idelvion

Sponsor: CSL Behring

September 2017

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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

About AusPARs

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

Contents

Common abbreviations

Abbreviation	Meaning
AE	Adverse Event
ALT	Alanine Transaminase
aPPT	Activated Partial Thromboplastin Time
AST	Aspartate Transaminase
AUC	Area Under the Concentration vs. Time Curve
BUN	Blood Urea Nitrogen
C_{max}	Maximum Concentration
ECG	Electrocardiograph
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
FIX	Factor IX
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IU	International Units
LDH	Lactate Dehydrogenase
LFTs	Liver Function Tests
pdFIX	Plasma-derived factor IX
PI	Product Information
PK	Pharmacokinetics
PT	Prothrombin Time
PTP	Previously Treated Patient
PUP	Previously Untreated Patient
rFIX	Recombinant factor IX
rIX-FP	Recombinant factor IX – fusion protein (Albutrepenonacog alfa)

Abbreviation	Meaning
SAE	Serious Adverse Event
TAT	Thrombin-Antithrombin Complex
TGA	Therapeutic Goods Administration
WBC	White Blood Cell

I. Introduction to product submission

Submission details

Type of submission:	New biological entity
Decision:	Approved
Date of decision:	14 September 2016
Date of entry onto ARTG	20 September 2016
Active ingredient(s):	Albutrepenonacog alfa (rch)
Product name(s):	Idelvion
Sponsor's name and address:	CSL Behring (Australia) Pty Ltd 189-190 Camp Rd Broadmeadows VIC 3047
Dose form(s):	Powder and solvent for injection,
Strength(s):	250, 500, 1000 or 2000 IU
Container(s):	Glass vial
Pack size(s):	1 (composite pack containing powder and water for injection with an administration pack[1])
Approved therapeutic use:	*Idelvion is proposed for indication in all patients with haemophilia B for:* *- routine prophylaxis to prevent or reduce the frequency of bleeding episodes* *- control and prevention of bleeding episodes* *- control and prevention of bleeding in the perioperative setting*
Route(s) of administration:	Intravenous (IV)
Dosage:	The Dosage recommendations are complex, varying with Indication, patient age group, and individual patient characteristics.
ARTG number (s):	255552, 259938, 259939, 259940

[1] Containing: I filter transfer device 20/20
I disposable 5 or 10 mL syringe
I venipuncture set
2 alcohol swabs
I non-sterile plaster

Product background

This AusPAR describes the application by the sponsor to register Idelvion (albutrepenonacog alfa (rIX-FP, CSL654)), a coagulation Factor IX (FIX) product in which recombinant human FIX is genetically fused to recombinant human albumin to improve its pharmacokinetic profile, thereby prolonging clotting activity. The sponsor has proposed the following indications for intravenous (IV) use in adults and children (minimum age undefined):

Idelvion is indicated in all patients with haemophilia B for:

- *Routine prophylaxis to prevent or reduce the frequency of bleeding episodes*
- *Control and prevention of bleeding episodes*
- *Control and prevention of bleeding in the perioperative setting*

Albutrepenonacog is a fusion protein produced by recombinant DNA technology in a Chinese Hamster Ovary (CHO) cell line. Recombinant coagulation Factor IX protein is genetically fused to recombinant albumin. The rationale for combination with albumin is to prolong half-life and thus allow for an increased dosage interval. The linkage to albumin is cleaved when Factor IX is activated in vivo. The activity of Factor IX is detected in individual patients by clotting factor test activated partial thromboplastin time 'aPTT'.

The Dosage recommendations are complex, varying with Indication, patient age group, and individual patient characteristics (see PI Attachment 1). 'Prophylaxis' regimens were modified during the evaluation period, in response to evaluator comment and sponsor review.

The maximum recommended dose is 100 IU/kg (on alternate days) for treating a major bleed or for use during major surgery in patients under 12 years of age; otherwise typical doses are at lower maintenance levels of up to 40 IU/kg/week.

Regulatory status

This is an application for a new biological entity in Australia.

The TGA granted orphan drug designation for Idelvion on 27 October 2014 and the proposed indication is consistent with this designation.

At the time the TGA considered this application a similar application had been approved in the European Union (22 June 2015) and Canada (23 June 2016).

Health Canada approved the following Indication

Idelvion, Coagulation Factor IX (Recombinant), Albumin Fusion Protein (rIX-FP), is anantihemophilic factor indicated in patients with hemophilia B (congenital FIX deficiency) or Christmas disease for:

- *Routine prophylaxis to prevent or reduce the frequency of bleeding episodes*
- *Control and prevention of bleeding episodes*
- *Control and prevention of bleeding in the perioperative setting'*

The product monograph states that the recommended dose regimen for paediatric patients is the same as for adults.

The FDA approved Indications and Usage text reads:

> *Idelvion, Coagulation Factor IX (Recombinant), Albumin Fusion Protein (rIX-FP), a recombinant human blood coagulation factor, is indicated in children and adults with haemophilia B (congenital Factor IX deficiency) for:*

- *On-demand treatment and control of bleeding episodes*
- *Perioperative management of bleeding*
- *Routine prophylaxis to reduce the frequency of bleeding episodes in children and adults with hemophilia B (congenital Factor IX deficiency).*

Limitations of Use: Idelvion is not indicated for immune tolerance induction in patients with Hemophilia B.

Dosage includes Routine prophylaxis: 'For patients ≥12 years of age, the recommended dose is 25-40 IU Idelvion per kg body weight every 7 days. Patients who are well-controlled on this regimen may be switched to a 14- day interval at 50 to 75 IU Idelvion per kg body weight [see Clinical Studies (14)]. For patients < 12 years of age the recommended dose is 40-55 IU/kg body weight every 7 days.

The EU Therapeutic indications text reads:

Treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency).

Idelvion can be used for all age groups.

Posology includes Prophylaxis 'For long-term prophylaxis against bleeding in patients with severe hemophilia B, the usual doses are 35 to 50 IU/kg once weekly. Some patients who are well-controlled on a once-weekly regimen might be treated with up to 75 IU/kg on an interval of 10 or 14 days (see section 5.1).

In some cases, especially in younger patients, shorter dosage intervals or higher doses may be necessary. After a bleeding episode during prophylaxis, patients should maintain their prophylaxis regimen as closely as possible, with 2 doses of Idelvion being administered at least 24 h apart but longer as deemed suitable for the patient.

For routine prophylaxis the recommended dose regimen for paediatric subjects is 35 to 50 IU/kg once weekly (see sections 5.1 and 5.2).

Currently approved medicines for treatment of Haemophilia B in Australia are listed in Table 1.

Table 1: Currently approved medicines for treatment of Haemophilia B

Generic	Trade-name	Sponsor	TGA approved indication related to Haemophilia B
Plasma-derived FIX	Monofix-VF	CSL Ltd	MonoFIX-VF is indicated for the treatment of haemorrhages, for use in surgery, and as prophylaxis in patients with haemophilia B. MonoFIX-VF is not indicated for the treatment factor II, VII or X deficiencies because it does not contain therapeutic levels of these coagulation factors. MonoFIX-VF is not indicated for the treatment of haemophilia A patients with factor VIII inhibitors.
Recombinant FIX, nonacog alfa	BeneFIX	Pfizer Australia Pty Ltd	BeneFIX is indicated for the control and prevention of haemorrhagic episodes in patients with haemophilia B (congenital factor IX deficiency or Christmas disease), including control and prevention of bleeding in surgical settings. BeneFIX is not indicated for the treatment of other factor deficiencies (e.g. factors II, VII and X), nor for the treatment of

Generic	Trade-name	Sponsor	TGA approved indication related to Haemophilia B
			haemophilia A patients with inhibitors to factor VIII, nor for the reversal of coumarin induced anti-coagulation, nor for the treatment of bleeding due to low levels of liver-dependent coagulation factors.
Recombinant FIX, nonacog gamma	Rixubis	Baxalta Australia Pty Ltd	(1) Routine prophylaxis of bleeding episodes in adults with haemophilia B (2) Treatment and prevention of bleeding episodes in adults with haemophilia B (congenital factor IX deficiency)(3) Peri-operative management in adults with haemophilia B
Recombinant FIX bound to Fc fragment of IgG1, eftrenonacog alfa (rhu)	Alprolix	Biogen Australia Pty Ltd	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) Comment: Alprolix has a prolonged half-life of 84 h compared to 24 h for the other products; it has a dosing interval of up to 48 h for bleeding episodes and surgical prophylaxis, and up to 10 days for routine prophylaxis.

Product Information

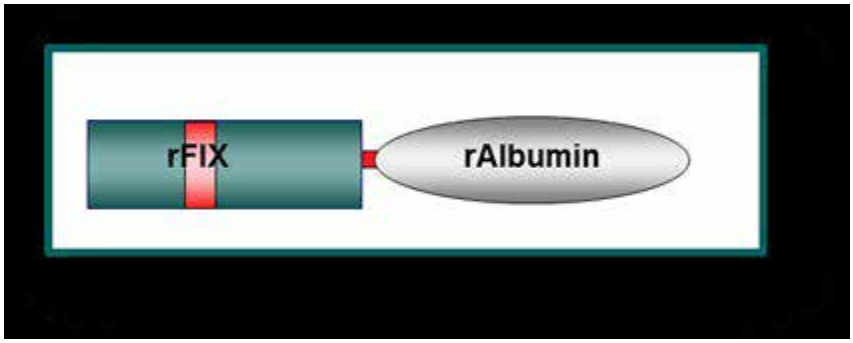
The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Quality findings

Drug substance (active ingredient)

Full length rIX-FP is expressed as a single chain glycopeptide of 1018 amino acids with a molecular weight of approximately 125 kilo Daltons (kDa). The primary amino acid sequence is comparable to the most prevalent Thr148 allelic form of native FIX. rIX-FP was generated by the genetic fusion of human albumin to FIX. FIX complementary DNA (cDNA) was joined to human albumin cDNA by a FIX-derived cleavable linker sequence (Figure 1).

Figure 1: Schematic diagram of rIX-FP



Drug product

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. The product is not photo-stable.

In-use stability data have also been submitted. The proposed shelf-life of 36 months for rIX-FP for the fill sizes 1000 IU and 2000 IU and 24 months[2] for 250 IU and 500 IU under recommended storage conditions of + 2°C to + 25°C is supported by stability results of several initiated long term studies performed with pilot and commercial scale batches manufactured during process development of the drug product.

Stability studies have been conducted in accordance with relevant International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines.

When the lyophilized DP was exposed to high temperature and related potential photolysis, less degradation was observed compared to reconstituted DP, confirming the protective effect of lyophilisation on rIX-FP.

All results are within specifications with one exception. The factor IX potency and therefore the specific activity did not meet specification after one week light exposure in primary packaging.

The data obtained support the assumption that light exposure according to ICH Q1B does have a negative impact on the activity of this product. This product must be protected from light.

rIX-FP is physicochemical stable for up to 8 h in solution upon reconstitution, however the presentation contains no preservatives and therefore from a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use should not be longer than 4 h at maximum +25°C. These proposed storage periods are fully supported by the data provided.

Potency is assayed using a one stage clotting assay (aPTT) (European Pharmacopeia (Ph. Eur)). The assay for Coagulation Factor IX is executed in the presence of Factor IX deficient plasma.

Quality summary and conclusions

There are no objections on quality grounds to the approval of Idelvion rIX-FP (albutrepenonacog alfa).

2 All fill sizes now have an approved 36 month shelf life in Australia.

Proposed conditions of registration for clinical delegate

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

   The sponsor must supply:

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

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

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

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

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

III. Nonclinical findings

Introduction

The quality of the nonclinical dossier for Idelvion was acceptable. The submitted safety and toxicity studies were performed according to Good Laboratory Practice (GLP) and were consistent with ICH guideline S6 (R1) for biotechnology-derived therapeutic products.[3] In view of its relationship to existing approved human FIX products on the register (MonoFIX-VF and BeneFIX) the nonclinical data focussed on a comparison of the pharmacodynamic (clotting efficacy) and pharmacokinetic characteristics (elimination half-life) of rIX-FP with the recombinant human FIX product, BeneFIX. Idelvion is the second pharmacokinetically modified FIX product to be submitted for registration. Alprolix, consisting of recombinant FIX covalently linked to the fusion protein Fc of immunoglobulin G, was registered in May 2014.

All animal studies used the clinical (IV) route of administration. Repeat-dose toxicity studies were conducted in rats and monkeys, as these species were pharmacologically responsive to rIX-FP. Determination of safety pharmacology parameters were intended to be incorporated into these studies, with only respiratory safety studied in a dedicated study. All repeat-dose toxicity studies included toxicokinetic and antibody monitoring. Additional studies submitted include genotoxicity, local tolerance and thrombogenic potential.

[3] Preclinical Safety Evaluation Of Biotechnology-Derived Pharmaceuticals S6(R1)

Pharmacology

Primary pharmacology

An in vitro study confirmed that rIX-FP was pharmacologically active in the coagulation system of rats, rabbits, monkeys and human (using activated partial thromboplastin time, aPTT, as the primary endpoint). Two animal models of human haemophilia B (FIX knockout mice and haemophilia B dogs) were selected to examine pharmacodynamic activity in vivo. Haemostatic efficacy, comparable to that of BeneFIX, was demonstrated in both models using the clinical (IV) route. In haemophilia B dogs, the pharmacodynamic effect of rIX-FP was shown to be more prolonged than that of BeneFIX, with a 3 to 4 day delay in reversal of improved clotting function in the rIX-FP treated group. Pharmacokinetic data indicated that clearance of rIX-FP was more than 3 times longer than for BeneFIX, confirming the improved pharmacokinetic profile and accounting for the more prolonged pharmacodynamic effect. In the dog study, the development of neutralising antibodies was reported in both treatment groups (that is, rIX-FP and BeneFIX). Furthermore, two animals in the dog study (one treated with rIX-FP and one with BeneFIX) developed haematomas and had prolonged coagulation time (measured as aPTT) and experienced a clinical bleed (a hematoma). As neither animal ultimately responded to medical treatment (application of normal canine plasma), both were euthanized 21 days after dosing due to concerns over animal welfare. As the appearance of inhibitory anti-drug antibodies could be confirmed in these animals, cross-reactivity of these neutralizing antibodies against the canine FIX accounted for this non-responsiveness of the treatment with normal canine plasma.

Secondary pharmacodynamics and safety pharmacology

The absence of secondary pharmacodynamic studies is not considered to be a deficiency based on the mechanism of action of rIX-FP. A respiratory study in conscious rats was the only dedicated safety pharmacology study submitted. Cardiovascular safety was examined in the 4 week repeat dose study in monkeys, in which electrocardiogram (ECG) parameters and blood pressure were monitored. No evidence of secondary pharmacodynamic activity was observed in these studies. Evidence of central nervous system (CNS) safety is provided by the absence of clinical signs, macroscopic and histopathological findings in the repeat dose toxicity studies in rats and monkeys, which is not unexpected based on the inability of rIX-FP to penetrate the blood brain barrier as shown in the tissue distribution study. In addition, thrombogenic potential (which has been associated with donor derived FIX products) was not observed in a rabbit model. Overall, based on the type of submission, the data submitted provided adequate evidence of a lack of potential for off target pharmacodynamic activity.

Pharmacokinetics

The pharmacokinetics of rIX-FP was evaluated in single dose studies in rats, haemophilia B dogs and monkeys, and in repeat dose studies in rats and monkeys, using enzyme-linked immunosorbent assay (ELISA) assays. Studies demonstrated that systemic exposures (peak plasma concentration (C_{max}) and area under the concentration versus time curve (AUC)) following IV administration were generally higher after administration of BeneFIX. Plasma clearance for rIX-FP was slower than the corresponding values for BeneFIX in rats and dogs, with values approximately 3 fold smaller in the latter species. Similarly, the plasma half-life of rIX-FP in haemophilia B dogs was longer than that of BeneFIX. The C_{max} and AUC of rIX-FP were dose-proportional and showed no evidence of gender dependence in any species.

The steady state volume of distribution indicated a predominantly vascular localisation for rIX-FP and consistent with this, the tissue distribution study found high concentrations of radioactivity predominantly in well vascularised tissues and excretory organs only. The tissue distribution was comparable to that of BeneFIX, indicating that it was not altered by albumin fusion. Both rIX-FP and BeneFIX were detected in bone marrow and in synovial or mineralised regions of the knee joint, predominantly localised in the growth plate regions of the long bones. The time course for radioactivity detection was similarly long following IV administration of radiolabelled rIX-FP and albumin, with both detectable over 120 h, while BeneFIX-derived radioactivity was only detectable over 24 h. This supports the hypothesis that albumin fusion is responsible for the prolonged tissue half-life of rIX-FP.

The metabolism of rIX-FP was not investigated. As human plasma proteins, recombinant FIX and albumin are expected to be metabolised in the same manner as the endogenous proteins. Following administration of single IV dose of rIX-FP to male rats the major route of elimination was urinary, with 73% of the dose eliminated in urine and a total of 80.8% of dose eliminated after 240 hours. High-performance liquid chromatography (HPLC) analysis of urinary radioactivity confirmed that the excreted components were low molecular weight components (<1 kD) and matched that observed following IV administration of BeneFIX.

The development of anti-human FIX antibodies can be a problem for nonclinical repeat-dose toxicity studies. Inhibitory antibodies were formed in the pharmacology study in haemophilia B dogs following administration of a single dose of rIX-FP (and BeneFIX) but there was no evidence of an antibody response to either human FIX or human albumin following administration of single doses of rIX-FP to monkeys. However, an antibody response was observed in the 4-week repeat-dose studies in both rats and monkeys.[4] In both species, antibodies to both human FIX and human albumin were shown to develop with increasing incidence during the course of the studies. In the monkey study, the development of antibodies correlated with reduced exposure (plasma AUC), presumably due to the increased clearance of antigen-antibody complexes.

Toxicology

Acute toxicity

Single IV doses of up to 500 IU/kg were well tolerated in rats and monkeys, with no toxicologically significant findings. An additional single dose study in rats compared the toxicity of pilot and commercial scale batches, and found no notable difference.

Repeat-dose toxicity

Two repeat-dose studies were submitted to evaluate the toxicity of rIX-FP in rats and cynomolgus monkeys. The maximum dose of 500 IU/kg is 5 times the maximum proposed clinical dose for acute treatment, and 12.5 times the maximum proposed prophylactic dose. Both studies were up to 4 weeks in duration and included an interim 6 day sacrifice due to a potential development of an immune response against the human protein components of rIX-FP. The animals were dosed by the clinical route. Daily dosing is not proposed clinically, with weekly or fortnightly dosing recommended for routine prophylactic use but acute treatment for major surgery may require dosing on alternate days. The daily dosing was appropriate because the plasma half-life was shorter in the

[4] At the end of the study, anti-human FIX antibodies could be detected in 12 monkeys (67%), whilst one monkey (6%) also had antibodies against human albumin.

nonclinical species. The duration of the studies is relatively short considering indication for chronic use but this is considered to be appropriate because of the development of antibodies to the heterologous proteins being administered. Overall, the study design was consistent with the relevant EU guideline.[5]

Relative exposure

The following table (Table 2) shows the relative exposure in the animal studies.

Table 2: Relative exposure in single and repeat-dose toxicity studies

Species	Study duration Study no.	Day	Dose IU/kg/ day	AUC_{0-t} ^ IU·h/mL	C_{max} IU/mL	Exposure ratio based on:	
						AUC#	C_{max}#
Rat (SD)	1 day	1	75	19.9	1.02	0.17	0.93
			150	35.5	2.38	0.30	2.18
			500	117	6.96	0.98	6.38
Rat (SD)	4 weeks	28	75	9.15	1.13	0.08	1.0
			150	32.2	2.80	0.27	2.6
			500	75.1	9.23	0.63	8.5
Monkey Cynomolgus	4 weeks	1	75	16.1	1.04	0.13	0.95
			150	32.2	2.06	0.27	1.9
			500	108.3	7.82	0.90	7.2
		28	75	46.6	2.61	0.39	2.4
			150	79.5	4.30	0.66	3.9
			500	273	16.63	2.3	15.2
Human (haemophilia B)	Single dose Study; Santagostino *et al* 2012		100	120	1.09	–	

= animal: human plasma AUC or C_{max}; ^ = data are for the sexes combined; Day 1 monkey data are $AUC_{0-24h;}$ human and Day 1 rat data are $AUC_{0-\infty}$; Human AUC data based on doses of 50 and 75 IU/kg have been scaled, to the maximum proposed maintenance and acute treatment doses of 40 and 100 IU/kg, respectively (assuming a linear increase in AUC with dose).
Santagostino, E. et al (2012). Safety and pharmacokinetics of a novel recombinant fusion protein linking coagulation factor IX with albumin (rIX-FP) in haemophilia B patients. Blood 2012; 120:2405-2411.

Exposure ratios have been calculated based on animal: human plasma AUC and C_{max} values. The animal AUC values were based on plasma concentration measurements taken up to 120 h (rats) and 240 h (monkeys), while the human AUC data were extrapolated to infinity. Therefore, exposure comparisons have been made based on both AUC and C_{max}.

[5] EMA/CHMP/ICH/731268/1998 ICH6 (R1)-preclinical safety evaluation of biotechnology-derived pharmaceuticals

The proposed recommended dose in haemophilia B patients depends on clinical need, with a lower dose administered for routine prophylaxis compared with acute need such as major surgery. Relative exposure comparisons are based on the highest proposed acute dose of 100 IU/kg. When based on AUC, relative exposures were mostly subclinical, but were close to unity (with a maximum of 2) at the high dose level. When based on plasma C_{max}, relative exposures in the 4 week rat and monkey studies were up to 9 and 15, respectively. Taking into consideration the differences in dose interval and sampling times between the animal and human studies and the nature of the product, it is considered that exposures were generally adequate in the repeat-dose toxicity studies.

Major toxicities

There were no significant toxicities in the two 4 week repeat-dose studies in rats and monkeys. Two mortalities in rats treated with the high dose of 500 IU/kg/day for 28 days are only possibly associated with treatment, as no cause of death could be determined and there were no other treatment-associated adverse effects. Intravenous administration of rIX-FP was well tolerated in both species, with no evidence of adverse local or systemic effects. Thrombus was detected in lungs of 2 rats dosed with a low dose and one rat dosed with a mid-dose after 4 weeks of dosing in the 4 week study. Since no thrombus was seen in the high dose group and one control rat also had pulmonary thrombus at the interim sacrifice (6 days), and the same finding was not observed in monkeys, the low incidence of pulmonary thrombus in rats was probably not related to treatment. A thrombogenic study in rabbits indicated no thrombogenic potential.

The development of anti-human FIX and anti-human albumin antibodies precluded longer term toxicity studies in animals, as the number of antibody positive animals increased with dosing duration, and resulted in reduced exposure in those animals.

Genotoxicity

Genotoxicity studies are not considered to be essential for biotechnology derived products such as rIX-FP. Both FIX and albumin are normal components of human plasma, and therefore genotoxicity is not expected. The sponsor submitted a bacterial reverse mutation test and a chromosomal aberration test using human lymphocytes, both of which were negative.

Carcinogenicity

Carcinogenicity studies were not conducted with rIX-FP. This is in accordance with the ICH guideline for biotechnology-derived products[6] as the two components of rIX-FP are human recombinant proteins.

Reproductive toxicity

No reproductive toxicity studies were submitted. The sponsor justified this on the basis that the two components of rIX-FP are human recombinant proteins which are not known to have adverse developmental or reproductive effects, and haemophilia B almost exclusively affects males. In addition, there were no safety signals from single and repeat-dose toxicity studies suggestive of an adverse effect on reproductive health.

Pregnancy classification

The sponsor has not proposed a Pregnancy Category for rIX-FP. While the target patient population is almost exclusively male (owing to the sex-linkage of haemophilia B), there are some rare instances where females are affected. An appropriate category needs to 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

[6]Preclinical Safety Evaluation Of Biotechnology-Derived Pharmaceuticals S6(R1)

FIX (BeneFIX), have Category B2[7], on the basis that no animal reproductive studies have been conducted to determine effects on fetal development. Alprolix has a pregnancy Category of C[8], since it was shown to cross the placenta in mice.

Based on a lack of reproductive toxicity data for rIX-FP, pregnancy Category B2 is recommended.

Local tolerance

The clinical formulation was well tolerated in the rabbit following administration by the intravenous, intra-arterial and peri-venous routes and also in single and repeat-dose toxicity studies in rats and monkeys.

Paediatric use

rIX-FP is proposed for use in adults and children (minimum age not specified). No studies in juvenile animals were performed. Such studies would be technically challenging owing to the need to administer IV injections repeatedly in neonatal or young rodents. 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 submitted nonclinical dossier was in accordance with the relevant ICH guideline for the nonclinical assessment of biological medicines. The pivotal safety-related studies were GLP compliant and all animal studies used the clinical (IV) route of administration in rats and monkeys, as these species were pharmacologically responsive to rIX-FP.
- rIX-FP had similar clotting activity to the comparator, BeneFIX, in plasma from rats, rabbits, monkeys and human. Haemostatic efficacy, comparable to that of BeneFIX, was demonstrated in appropriate mouse and dog models of haemophilia B. Prolongation of the clotting activity in dogs was correlated with a more sustained increase in plasma FIX concentration compared with that observed with BeneFIX.
- Safety pharmacology assessment was adequate for the type of product and did not indicate any potential for adverse effects on the CNS, cardiovascular or respiratory systems.
- Systemic exposures to human FIX were generally higher for rIX-FP than after administration of BeneFIX; attributable to slower clearance and longer half-life of rIX-FP. The development of anti-FIX antibodies following repeated dosing in some animals reduced the systemic exposures of these individuals. However, in monkeys, mean exposures increased with repeated dosing, indicative of accumulation.
- The tissue distribution was comparable to that of BeneFIX, indicating that it was not altered by albumin fusion. However, the elimination of radioactivity was slower than

[7] Category B2: Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed.
Studies in animals are inadequate or may be lacking, but available data show no evidence of an increased occurrence of fetal damage.
[8]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.

that of BeneFIX, but was comparable to that observed following IV administration of radiolabelled albumin, suggesting that albumin fusion is responsible for the prolonged tissue half-life of rIX-FP.

- The metabolism of rIX-FP was not investigated, which is acceptable. Following IV dosing with radiolabelled rIX-FP, 73% of the dose was eliminated in urine within 240 h.
- Single IV doses of up to 500 IU/kg were well tolerated in rats and monkeys with no toxicologically adverse findings.
- Repeat-dose toxicity studies by the IV route were conducted in rats and cynomolgus monkeys, with daily doses administered for up to 4 weeks. The relative systemic exposure achieved in these studies is considered to be adequate. Antibody formation was observed in both species.
- rIX-FP did not show thrombogenic potential in a rabbit model.
- rIX-FP was negative in a bacterial reverse mutation test and a chromosomal aberration test using human lymphocytes. Carcinogenicity was not investigated, which is consistent with ICH S6 (R1).
- The clinical formulation was well tolerated in a local tolerance study in the rabbit following administration by the intravenous, intra-arterial and peri-venous routes and also in single and repeat-dose toxicity studies in rats and monkeys.
- Overall, there are no nonclinical objections to registration. Changes to the Product Information recommended have been made by the sponsor in the updated document submitted on 4 April 2016, with the exception of the inclusion of a Use in Pregnancy category. Category B2 is recommended based on a lack of nonclinical data.

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

Clinical rationale

Haemophilia B is an X-linked congenital bleeding disorder caused by a deficiency of FIX. It is characterised by recurrent bleeding episodes, typically into joints and muscles. It is less common than haemophilia A (factor VIII deficiency), accounting for 15-20% of all haemophilia cases.[9] The Haemophilia Foundation of Australia estimates that there are approximately 2,950 subjects with haemophilia in Australia.[10] The prevalence of haemophilia B in Australia would therefore be approximately 442 to 590 subjects. Haemophilia is often classified as mild, moderate or severe based on factor levels.

[9] World Federation of Hemophilia. Guidelines for the Management of Hemophilia (2nd edition). 2012. Available from: http://www.wfh.org/en/resources/wfh-treatment-guidelines
[10] Haemophilia Foundation Australia. *Haemophilia* [online] March 2015 [viewed 29 October 2015]. Available from: https://www.haemophilia.org.au/bleedingdisorders/haemophilia

Table 3: Classification of Severity of Haemophilia

SEVERITY	CLOTTING FACTOR LEVEL	BLEEDING EPISODES
Severe	< 1 IU/dl (< 0.01 IU/ml) or < 1 % of normal	Spontaneous bleeding into joints or muscles, predominantly in the absence of identifiable hemostatic challenge
Moderate	1-5 IU/dl (0.01-0.05 IU/ml) or 1-5% of normal	Occasional spontaneous bleeding; prolonged bleeding with minor trauma or surgery
Mild	5-40 IU/dl (0.05-0.40 IU/ml) or 5-<40% of normal	Severe bleeding with major trauma or surgery. Spontaneous bleeding is rare.

The current standard treatment of haemophilia B is based on the use of replacement FIX therapy. Replacement therapy products that are currently registered in Australia are:

- Plasma-derived FIX (Monofix-VF, CSL Ltd) which is manufactured from blood donated to the Australian Red Cross Blood Service;
- Recombinant FIX (nonacog alfa; Benefix; Pfizer Australia Pty Ltd);
- Recombinant FIX (nonacog gamma; Rixubis; Baxalta Australia Pty Ltd); and
- Recombinant long-acting FIX (eftrenonacog alfa; Alprolix; Biogen Australia Pty Ltd).

The FIX contained in Monofix-VF, Benefix and Rixubis 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 12-24 h. For routine prophylaxis, dosing is recommended twice per week.[11]

Alprolix is another long-acting form of recombinant FIX in which the FIX molecule is bound to the Fc fragment of an immunoglobulin G1 (IgG1) molecule. It has a half-life of 82 h. For the treatment of bleeding episodes and for surgical prophylaxis the dosing interval is up to 48 h, and for routine prophylaxis, the recommended dosing interval is up to 10 days.[12]

Combining the FIX molecule with an albumin molecule is intended to produce a prolonged half-life, with less frequent dosing required. The draft PI states that albutrepenonacog alfa has an elimination half-life of 104 h and the recommended dosage interval for the treatment of bleeding episodes and surgical prophylaxis is up to 72 h. The recommended initial dosage interval for routine prophylaxis is up to 14 days.

Guidance

The following 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;[13]

[11] Therapeutic Goods Administration. MonoFIX-VF Product Information [online] 30 July 2015 [viewed 29 October 2015]. Available from: https://www.ebs.tga.gov.au/
Therapeutic Goods Administration. Benefix Product Information [online] 15 August 2013 [viewed 29 October 2015]. Available from: https://www.ebs.tga.gov.au/
Therapeutic Goods Administration. Rixubis Product Information [online] 27 May 2015 [viewed 29 October 2015]. Available from: https://www.ebs.tga.gov.au/
[12] Therapeutic Goods Administration. Alprolix Product Information [online] 15 July 2015 [viewed 29 October 015]. Available from: https://www.ebs.tga.gov.au/
[13] European Medicines Agency. Guideline On The Clinical Investigation Of The Pharmacokinetics Of Therapeutic Proteins (CHMP/EWP/89249/2004); 2007. Available from: http://www.tga.gov.au/clinical-efficacy-and-safety-guidelines

– Guideline on clinical investigation of recombinant and human plasma-derived factor IX products (EMA/CHMP/BPWP/144552/2009); 2011.[14]

The 2011 guideline on Factor IX products has recently been updated.[15] However, this revised version did not come into effect until September 2015, after the sponsor had completed the pivotal studies contained in this submission.

Compliance with these guidelines will be considered in the relevant sections of this report.

Contents of the clinical dossier

Scope of the clinical dossier

The submission contained the following clinical information:

- 1 Phase I safety and PK study using ascending single doses (Study 2001);
- 1 population pharmacokinetic analysis;
- 1 Phase I/II study examining PK, safety and efficacy (Study 2004);
- 1 pivotal Phase II/III PK, efficacy and safety study in adults and adolescents (Study 3001):
- 1 pivotal Phase III PK, efficacy and safety study in children (Study 3002);
- 1 Phase III extension efficacy and safety study (Study 3003).
- Tabulated data for pooled analyses of PK, efficacy and safety;
- Literature references.

Paediatric data

The submission included paediatric pharmacokinetic, efficacy and safety data (study 3002).

Good clinical practice

The clinical study report for each of the submitted studies included an assurance that they were carried out in accordance with the ICH (International Conference on Harmonization) Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki.

Pharmacokinetics

Studies providing pharmacokinetic data

Four of the five submitted clinical studies provided PK data. Table 4 shows the studies relating to each pharmacokinetic topic and the location of each study summary.

[14]European Medicines Agency. Guideline on clinical investigation of recombinant and human plasma-derived factor IX products (EMA/CHMP/BPWP/144552/2009); 2011. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000388.jsp&mid=WC0b01ac0580032ec8

[15] European Medicines Agency. Guideline on clinical investigation of recombinant and human plasma-derived factor IX products (EMA/CHMP/BPWP/144552/2009 rev 1); 2015. Available from: http://www.tga.gov.au/clinical-efficacy-and-safety-guidelines

Table 4: Submitted pharmacokinetic studies

PK topic	Subtopic	Study ID	*
PK in adults and adolescents with haemophilia B	General PK Single dose	2001	*
		2004	
		3001	
	Repeat-dose	3001	
PK in children with haemophilia B	General PK Single dose	3002	*
Population PK analyses		RA21020032	*

* Indicates the primary aim of the study.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

Evaluator's conclusions on pharmacokinetics

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

The data demonstrate that administration of rIX-FP is associated with restoration of FIX activity in plasma in subjects with severe FIX deficiency. This FIX activity in plasma is prolonged when compared to conventional FIX replacement products such as rFIX and pd-FIX. Compared to adults, children have increased clearance of rIX-FP and a higher volume of distribution, and as a result achieve lower plasma FIX activity levels.

rIX-FP was associated with a higher incremental recovery than the comparator FIX products used in the submitted studies.

Pharmacodynamics

FIX activity was measured in four of the five studies submitted. In haemophilia B studies this is considered to be a pharmacokinetic endpoint and results have therefore been described above in section 4 of this report. There were no other PD data submitted.

Dosage selection for the pivotal studies

The doses used in the pivotal studies were based on PK data from the Phase I PK study (Study 2001). For Study 3001, doses were calculated using the formula

> *Required dose (IU) = [Desired increase in FIX levels (IU/dL) ÷ incremental recovery (IU/dL per IU/kg)] X weight (kg).*

For Study 3002 prophylaxis dose was set at 35-50 IU/kg every 7 days, which could be adjusted based on the individual subject's PK data. Target FIX activity levels for the

treatment of bleeding episodes were based on the recommendations of the World Federation of Haemophilia (WFH).

The dosage regimens recommended in the draft PI for the treatment of bleeding episodes and use in surgery are not identical to those used in the pivotal studies. Rather the sponsor has incorporated the incremental recovery values obtained from the PK assessments in the studies into a dosing formula to obtain desired plasma FIX activity levels. This is an acceptable approach used with other FIX products.

Efficacy

Studies providing efficacy data

See *Scope of clinical dossier* above.

Evaluator's conclusions on efficacy

The pivotal studies complied with the requirements of the EMA guideline for Factor IX products. The guideline states that pharmacokinetic endpoints such as incremental recovery, half-life, AUC and clearance are important surrogate endpoints for efficacy for a FIX product. As described in section Pharmacokinetics (Attachment 2) of this report, the PK data for rIX-FP indicate that the product restores FIX activity to plasma of subjects with severe FIX deficiency, with a half-life that is prolonged compared to conventional FIX products.

As recommended by the EU guideline, the two pivotal studies were conducted in previously treated patients (PTPs).

Study 3001 examined efficacy in adults and adolescents. This study demonstrated that switching subjects from an on-demand regimen with rIX-FP to a prophylaxis regimen resulted in a significant reduction in the incidence of spontaneous (and total) haemorrhages. It also demonstrated that in certain subjects, the dosage interval for prophylaxis could be extended to 10 or 14 days without a notable increase in the frequency of bleeding episodes.

For the treatment of mild or moderate bleeding, 98.6% of episodes could be managed with 1 or 2 infusions of rIX-FP. Efficacy of rIX-FP in the treatment of bleeding was assessed as excellent or good in 94.2% of episodes by the investigators, and 94.1% of episodes by the subjects. In this study there were no episodes of major bleeding.

Study 3002 examined efficacy in paediatric subjects aged < 12 years. In this study a prophylaxis regimen using a 7 day dosage interval was found to be associated with a low rate of spontaneous haemorrhage.

For the treatment of bleeding, 97.2% of episodes could be managed with 1 or 2 infusions of rIX-FP. Efficacy of rIX-FP in the treatment of mild or moderate bleeding was assessed as excellent or good in 96.2% of episodes by the investigators. Efficacy was also assessed as good in 2 episodes of major bleeding.

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

Efficacy in surgery was assessed in a total of 15 surgeries in 13 subjects. Where the investigator reported on overall assessment of haemostasis, the assessments were 'excellent' or 'good' in all cases.

Limitations of the efficacy data were assessed to be:

1. One of the proposed dosage regimens for prophylaxis therapy in the draft PI is 50 to 75 IU every 14 days. The text implies that subjects can commence prophylaxis with rIX-FP using this regimen. The efficacy data do not support such an approach. In Study 3001 all subjects commenced prophylaxis with a 7day dosage interval and only those subjects who met certain criteria could be transitioned to a 10 or 14 day dosage interval (see section Pivotal efficacy study in Attachment 2). It is likely that a 14 day regimen will have reduced efficacy in subjects who do not meet these criteria. Therefore the use of a 14 day dosage interval should be similarly restricted in the PI.
2. For prophylaxis, a dosage interval of more than 7 days has not been studied in children aged < 12 years. The sponsor is proposing that a suitable prophylaxis regimen for use in this group is 50 to 75 IU/kg every 14 days. The population PK modelling suggests that the median trough FIX activity level in children will be lower than adults due to increased clearance. With a 14 day dose interval, there is a risk that the efficacy of prophylaxis will be reduced in children compared to that seen in adolescents and adults in Study 3001. Prophylaxis regimens have traditionally aimed to maintain a FIX activity level of > 1% at trough. Bleeding episodes are observed infrequently in subjects who are able to maintain such levels.[16] According to the population PK model, the predicted median trough level of FIX activity in subjects aged 0-6 years receiving the proposed regimen of 50 IU/kg every 14 days is only 1.1%. A sizeable proportion of these subjects are therefore likely to develop trough levels of < 1%. In the absence of clinical evidence of efficacy, the dosage interval for prophylaxis in children aged < 12 years should be limited to 7 days.
3. The EMA guideline requires that efficacy in the surgical setting should be studied in at least 10 major surgeries (in at least 5 separate individuals). Although efficacy of rIX-FP has been studied in 15 surgeries in total, many of these appeared to be fairly minor procedures, and it seems unlikely that the EMA minimum requirements have been met. The sponsor should be asked to identify which of the 15 procedures it considers to be 'major' and provide a definition of what constitutes major surgery. (See Attachment 2 (Second round evaluation) for sponsor's response)
4. Efficacy has not been studied in previously untreated patients (PUPs). The EU guideline does not require a study in PUPs prior to initial marketing approval for a novel FIX product; however it does suggest that such a trial should be conducted and submitted at a later time. The sponsor is planning to study PUPs in Study 3003.
5. No studies were submitted examining efficacy in patients with inhibitors.

Safety

Safety issues associated with FIX products in general include:

- Immunogenicity, including inhibitor development and allergic reactions (e.g. anaphylaxis);
- Thrombogenicity;
- Fevers, chills etc.

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

Studies providing safety data

All five studies submitted provided safety data. In the sponsor's Summary of Clinical Safety, a pooled analysis of safety data from Studies 2001, 2004, 3001 and 3002 was provided. Data from the ongoing Study 3003 was presented separately. 76 of the 80 subjects enrolled in Study 3003 had been previously treated with rIX-FP in one of the earlier studies. Only 4 new subjects were enrolled (all in Arm 3). The pooled analysis has been used as the primary basis for the review of safety in this report.

In the pivotal efficacy studies (3001-3002), the following safety data were collected:

- General adverse events (AEs) were assessed on an ongoing basis throughout the studies. At each visit, investigators specifically inquired (via non-leading questioning) about any AEs that might have occurred since the last visit. AEs were classified according to severity (mild, moderate or severe) and causality (not related, unlikely to be related, possibly related, probably related, and related).
- AEs of special interest were immunogenic events (e.g. inhibitor development), hypersensitivity events and thrombogenic events.
- Immunogenicity testing (for more details see Attachment 2).

Patient exposure

The pooled safety population (from Studies 2001, 2004, 3001 and 3002) included a total of 107 unique subjects. The extension Study 3003 is still ongoing. All subjects were treated with rIX-FP and no comparators or placebos were used. In some studies, subjects also received a single dose of their prior FIX product to enable a comparison of PK parameters.

In the pooled safety population, the median number of exposure days (EDs) was 63.0. A total of 75 subjects had at least 50 EDs, and 16 subjects had at least 100 EDs. The median number of days on study was 469.0. In the ongoing Study 3003, extent of exposure was lower (median EDs = 21.0[17]).

Comment: The EMA guideline requires a total exposure of 40 subjects receiving > 50 EDs, including 10 subjects aged < 6 years and 10 subjects aged 6 to < 12 years. The actual numbers achieved in the rIX-FP clinical program (pooled safety population) were 75, 10 and 15.

Safety issues with the potential for major regulatory impact

Liver toxicity

There was no evidence of hepatotoxicity in the submitted studies. However, further details of the results of liver function tests performed in Study 3001 should be sought from the sponsor.

Haematological toxicity

There was no evidence of severe haematological toxicity. As described above there were 4 cases of anaemia in Study 3002 which are unexplained. Further information on these cases should be sought from the sponsor.

Serious skin reactions

No serious skin toxicity was observed in the submitted studies.

[17] Extracted from Study 3003 data cut-off date 28 July 2015

Cardiovascular safety

No cardiovascular toxicity was observed in the submitted studies.

Unwanted immunological events

Immunogenic AEs, including the development of inhibitors, have been summarised in Attachment 2.

Adverse events

Overall there was a low incidence of unwanted immunological events.

Postmarketing data

Not applicable.

Evaluator's conclusions on safety

The total number of subjects exposed to rIX-FP in the submitted clinical studies was approximately 110. The clinical safety database for the product is therefore small, but meets the EMA guideline requirements for extent of exposure for FIX products for the treatment of haemophilia B.

The major safety issue with FIX products is the development of inhibitors. No cases of inhibitor development were observed in the submitted studies of rIX-FP. However, only previously treated subjects at low risk of inhibitor development were enrolled in the submitted studies. The sponsor is conducting a study in previously untreated subjects, which will provide further information on this risk. Only one hypersensitivity reaction was observed. The symptoms and signs of this event appeared minor and there were no features of anaphylaxis. There were no thromboembolic AEs and monitoring of markers of activation of the coagulation system did not suggest any increased risk of such events, compared to other FIX products.

Pyrexia was reported very commonly among children in Study 3002. However, none of these events were assessed as being related to rIX-FP. The only treatment-related AE that occurred in more than one subject was headache.

Overall the safety profile of rIX-FP is considered acceptable.

First Round Benefit-Risk Assessment

First round assessment of benefits

The benefits of rIX-FP in subjects with haemophilia B are:

- Restoration of plasma factor IX activity. The duration of plasma FIX activity is prolonged when compared to conventional FIX products (either plasma-derived or recombinant);
- A reduction in the incidence of bleeding episodes when prophylaxis regimen is used;
- Control of bleeding episodes, usually with 1 or 2 injections only;
- Adequate control of bleeding during surgical procedures.

First round assessment of risks

The risks of rIX-FP in subjects with haemophilia B are:

- Probable risks of inhibitor development and hypersensitivity reactions;
- Other minor adverse events (such as headache).

First round assessment of benefit-risk balance

The benefit-risk balance of rIX-FP is favourable, for the treatment of bleeding episodes and for prophylactic treatment.

Experience with the use of rIX-FP in major surgical procedures is limited and may not justify the proposed indication of 'Control and prevention of bleeding in the perioperative setting' (See Attachment 2 (Second round evaluation) for sponsor's response).

First round recommendation regarding authorisation

It is recommended that the application be approved. Approval of the perioperative setting indication should be dependent upon the sponsor's response to the questions raised (Attachment 2, *Clinical questions*).

It is recommended that use of a prophylaxis regimen with a 14 day dosage interval in adults and adolescents should be restricted to subjects who have previously achieved very good control with a 7 day dosage interval. The 14 day dosage interval should not be approved for use in children aged < 12 years.

Second Round Evaluation of clinical data submitted in response to questions

For details of the Clinical questions, sponsor's responses and the evaluation of these responses please see Attachment 2.

Second Round Benefit-Risk Assessment

In addition to the already demonstrated efficacy and safety, the sponsor has satisfactorily demonstrated sufficient use in patients undergoing major surgery to permit approval in the peri-operative setting.

Second round recommendation regarding authorisation

It is recommended that the application be approved for the indication:

> *Idelvion is indicated for the treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency), including the peri-operative setting. Idelvion can be used in all age groups.*

V. Pharmacovigilance findings

Risk management plan

The sponsor initially submitted a Risk Management Plan (EU-RMP Version 1.0 (dated 20 February 2015, DLP 9 January 2015) and Australian-specific annex (ASA) Version 1.0 (dated 22 July 2015)) which was reviewed by the RMP evaluator.

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 5.

Table 5: Summary of ongoing safety concerns in EU-RMP 1.0 and ASA 1.0

Safety concern	Details
Important identified risks	None
Important potential risks	Hypersensitivity/anaphylactic reactions Development of inhibitors to FIX Development of non-inhibitory antibodies to product (rIX—FP) Development of antibodies against CHO host cell proteins Dosing errors based on variability in the assays used during treatment monitoring of FIX levels
Missing information	Experience in patients with a history of thrombosis Experience of inhibitor formation in PUPs Experience in pregnancy and lactation, including labour and delivery Experience in elderly patients (aged 65 years and above)

PUP=previously untreated patients

Pharmacovigilance plan

The sponsor proposes routine pharmacovigilance for all safety concerns and missing information items.

The sponsor proposes additional pharmacovigilance activities for the following concerns hypersensitivity/anaphylactic reactions, development of inhibitors to factor IX, development of antibodies against CHO host cell proteins, development of non-inhibitory antibodies to product (rIX-FP), and inhibitor formation in PUPs.

Risk minimisation activities

The sponsor proposes routine risk minimisation activities for all safety concerns.

Reconciliation of issues outlined in the RMP report

Table 6 summarises the first round evaluation of the RMP, the sponsor's responses to issues raised by the evaluator and the evaluation of the sponsor's responses."

Table 6: Reconciliation of issues outlined in the RMP Evaluation Report (Round 1)

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
Safety considerations may be raised by the nonclinical and	*The sponsor, CSLB, confirms that where relevant, questions and outcomes from other evaluation reports will be cross-referenced and addressed in the RMP*	The sponsor's response has been noted.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
clinical evaluators through the consolidated request and/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 Risk Management Plan, and any specific information needed to address this issue in the RMP. For any safety considerations so raised, please provide information that is relevant and necessary to address the issue in the RMP.	*responses also.* *Please note that an updated version of the EU-RMP is supplied in Module 1.8.2 to ensure currency of information and assist in addressing the S31 response. The Australia Specific Annex (ASA) has also been updated.*	
'Long-term use' should be added as Missing Information.	*As requested, CSLB confirms that 'Long-term use' is added to the ASA as Missing Information.*	This is considered acceptable in the context of this application.
'Effects on fertility' should be added as Missing Information.	*As requested, CSLB confirms that 'Effects on fertility' is added to the ASA as Missing Information.*	This is considered acceptable in the context of this application.
The sponsor should summarise the known information on thromboembolic events with regard to Idelvion use.	*There have been no treatment-emergent AE reports describing the development of thromboembolic events (TEEs) to Idelvion use during the clinical development program. However, TEE, as a known risk for other FIX products, is a potential risk following the administration of Idelvion. Therefore, thromboembolic events (TEEs) have been included as an Important Potential Risk and known information about TEEs has been summarised in the updated EU-RMP (version 2.0). The ASA has been updated accordingly to align with the updated EU-RMP. The Australian PI is also updated to include a statement in the 'Precautions' section on*	The sponsor's response has been noted.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	thromboembolic events (please refer response to question below).	
The sponsor should assign Study CSL654_3003 to the Missing Information item 'Long-term use'.	*As requested, CSLB confirms that study CSL654_3003 is added to the Missing Information item 'Long-term use' in ASA as the proposed additional PV activities.*	This is considered acceptable in the context of this application.
In the 'Precautions' section, under the 'Inhibitor formation' heading, PI should contain the risk factors for inhibitor development: FIX gene mutation; Family history; Non-Caucasian ethnicity; Polymorphisms in TNF-α or IL-10; Intensive high dose treatments; and Surgery.	*Currently, the Australian PI addresses the possibility of Inhibitor formation resulting from Idelvion use under the 'Precautions' section (sub-section 'Inhibitors') and under the 'Dosage and Administration' section (sub-section 'Monitoring'). These sections instruct the health care professional on how to monitor for inhibitor formation and subsequent actions.* *As identified in the question, the risk factors for inhibitor development in haemophilia patients may include both environmental and genetic factors. In recent years, numerous studies have reported that genetic risk factors, such as large deletions, nonsense mutations, polymorphisms in TNF-α or IL-10, may play an important role in inhibitor development in Haemophila A (HA).*[18,19] *In contrast, information regarding the risk factors for inhibitor development in Haemophilia B (HB) patients is scarce and mostly focused on the FIX gene mutation.*[20] *Some studies showed that a relationship may exist between the presence of major deletion mutations in a patient's FIX gene and an increased risk of inhibitor formation. It was also suggested that severe disease condition, African ancestry, age < 11, intensity/high dose of FIX administration may be associated with inhibitor development in HB patients (Zhou et al., 2015).*[21]	This is considered acceptable in the context of this application for RMP purposes, subject to approval by the Delegate.

[18] DiMichele D. Inhibitor development in haemophilia B: an orphan disease in need of attention. Br J Haem. 2007; 138 (3), 305–315.
[19] Ragni MV et al. Risk factors for inhibitor formation in haemophilia: a prevalent case-control study. Heamophilia 15(5):1074-1082
[20] Osooli M Berntorp E Inhibitors in haemophilia: what have we learned from registries? A systematic review Journal of internal medicine 277 (1), 1-1
[21] Zhou J, Ding Q, Chen Z et al. Risk factors associated with inhibitor development in Chinese patients with haemophilia B. Haemophilia 2015;21(4):e286-e293

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
	However, due to the relative infrequency of FIX inhibitor development, very few of these risk factors were further explored in HB patients. Known risk factors for FVIII inhibitors do not necessarily apply to FIX inhibitors, given the differences between the haemophilias in inhibitor epidemiology, natural history and immunological processes. More in vitro and in vivo studies are needed to improve the knowledge and determine inhibitor risks in HB patients. *CSLB therefore proposes not to include the risk factors listed in the question in the Idelvion PI due to the unconfirmed nature of these risk factors in HB patients, that the list may not be inclusive of all potential risk factors for HB patients and because the listed risk factors are not specific to Idelvion. Furthermore, CSLB believe that the information already proposed in the Australian PI provides appropriate guidance on the potential for inhibitor development and appropriate monitoring actions in a form that is consistent with other currently marketed products.*	
In the 'Precautions' section, under the 'Use in females' heading, the PI should include a summary of the safety data available for this age group, and if no data is available, a statement that no data is available (or a statement to that effect).	*CSLB would like to refer to those sub-headings within the 'Precautions' section of the PI stated as 'Effects on fertility', Use in pregnancy' and 'Use in lactation'. All these subsections refer to the use of Idelvion in females. The sub-sections state that no animal studies have been conducted pertaining to fertility, pregnancy and lactation respectively. The sub-sections 'Use in pregnancy' and 'Use in lactation' also contain the statement 'Based on the rare occurrence of haemophilia B in women, experience regarding the use of Idelvion during <pregnancy/lactation> is not available'. CSLB believe that these statements within the 'Effects on fertility', Use in pregnancy' and 'Use in lactation' sub-headings indicate that data is not available for use in women specifically, therefore the need for a separate 'Use in females' heading is not necessary. CSLB also acknowledges that a separate 'Use in females' heading does not appear in the Australian approved PIs for similar products.*	This is considered acceptable in the context of this application for RMP purposes, subject to approval by the Delegate.

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
In the 'Precautions' section, the PI should include a general statement on thromboembolic events and disseminated intravascular coagulation seen in Factor IX products, including the risk factors for thromboembolic events.	*As also directed by clinical evaluation report, Question 6, CSLB confirms that a general statement on thromboembolic events and disseminated intravascular coagulation has been inserted into the 'Precautions' section of the PI under the heading 'Thromboembolism'. The statement is comparable with the 'Thromboembolism' statement from the EU Idelvion draft EU Summary of Product Characteristics (SmPC) Section 4.4.*	This is considered acceptable in the context of this application for RMP purposes, subject to approval by the Delegate.
In the 'Precautions' section, the PI should include a statement that Idelvion is not indicated for immune tolerance induction.	*CSLB confirms that the following statement: 'The safety and efficacy of Idelvion for immune tolerance induction has not been established' has been added to the 'Precautions' section of the PI under sub-heading 'Inhibitors'. The statement will be in line with the 'Immune tolerance induction' statement from the EU Idelvion draft SmPC Section 4.4.*	This is considered acceptable in the context of this application for RMP purposes, subject to approval by the Delegate.
In the 'Dosage and Administration' section, the PI should include a statement on continuous infusion of this product.	*CSLB confirms that the following statement: 'The safety and efficacy of Idelvion administration by continuous infusion have not been established' has been added to the PI under sub-heading 'Continuous infusion' within the 'Precautions' section. CSLB believes the 'Precautions' section is a more suitable location for this statement.*	This is considered acceptable in the context of this application for RMP purposes, subject to approval by the Delegate.
In the 'Overdosage' section, the PI should contain the Poisons Information telephone number.	*CSLB has updated the 'Overdosage' section of the PI with the Poisons Information telephone number as follows:* *For general advice on overdose management:* *In Australia, contact the Poisons Information Centre on 131 126.* *In New Zealand, call the New Zealand Poisons Centre on 0800 POISON or 0800 764 766.*	This is considered acceptable in the context of this application for RMP purposes, subject to approval by the Delegate.
It is recommended to the Delegate that the draft consumer medicines information	*CSLB has updated the draft consumer medicines information document in accordance with the changes made to the Product Information document.*	This is considered acceptable in the context of this application for RMP purposes,

Recommendation in RMP evaluation report	Sponsor's response (or summary of the response)	RMP evaluator's comment
document be revised to accommodate the changes made to the product information document.		subject to approval by the Delegate.

Summary of recommendations

Outstanding RMP issues

Nil.

Outstanding PI/CMI recommendations to the Delegate

Nil.

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

Advice was not sought from ACSOM.

Key changes to the updated RMP

EU-RMP Version 1.0 (dated 20 February 2015, DLP 9 January 2015) and Australian-specific annex (ASA) Version 1.0 (dated 22 July 2015).

has been superseded by:

EU-RMP Version 2.0 (dated 29 January 2016, DLP 9 January 2015) and Australian-specific annex (ASA) Version 2.0 (dated 29 March 2016).

The following table (7) lists the key changes made to the RMP and ASA.

Table 7: Key changes to the EU-RMP and ASA

Summary of key changes between EU-RMP and ASA Version 1.0 and EU-RMP and ASA Version 2.0	
EU-RMP	Important Identified Risks added (previously listed as Important Potential Risks): · Hypersensitivity / anaphylactic reactions · Development of inhibitors to factor IX Important Potential Risks added: · TEEs (thromboembolic events) Missing Information added: · Experience in patients for ITI (off-label use) Pharmacovigilance plan: · Study CSL654_3003 added
ASA	Missing Information added for Australia only: · Effects on fertility · Experience in patients for Long-term use Pharmacovigilance plan: · Study CSL654_3003 added

Suggested wording for conditions of registration

RMP

Any changes to which the sponsor agreed become part of the risk management system, whether they are included in the currently available version of the RMP document, or not included, inadvertently or otherwise.

The suggested wording is:

> *Implement EU-RMP Version 2.0 (dated 29 January 2016, DLP 9 January 2015) and Australian-specific annex (ASA) Version 2.0 (dated 29 March 2016) and future updates where TGA approved, 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

The product is a purified protein manufactured using commercially available CHO host cells.

The coding sequence is derived from the predominant Thr148 allelic form of human native factor IX. The Factor IX (FIX) coding sequence was amplified and transferred into an expression vector. To extend FIX half-life, fusion proteins derived from genetic fusion of human FIX and albumin were generated.

A novel cleavable linker has been introduced in the amino acid sequence. This sequence is derived from a cleavage site in the activation sequence of the native FIX molecule. Computer analysis predicts that the linker sequence is likely to have a low immunogenic potential. Albumin cleavage in the presence of activated FXI was shown in vitro by incubation of fusion proteins with FXIa.

FIX coagulation activity is determined in a one-stage coagulation assay that measures shortening of the coagulation time in FIX deficient plasma. The activity of rIX-FP was determined by comparing the coagulation time with that of an in-house reference standard that has been calibrated against the current WHO FIX standard. This is the potency assay for this product, on which recommendations for clinical dosing is based.

The infectious disease safety evaluation asked questions relating to raw materials of animal origin including early exposure of CHO cell line and DNA vectors to bovine serum albumin. Following assessment of responses it was concluded that the evidence sufficiently demonstrated that risks relating to adventitious presence of infectious viral, prion and mycoplasma agents in the manufacturing of Idelvion had been controlled to an acceptable level.

All issues raised during evaluation were resolved. There were no objections to registration.

Excipients are tri-sodium citrate, polysorbate 80, mannitol and sucrose. The final product is a preservative free, sterile, lyophilised powder to be reconstituted with water for injection for intravenous injection.

The evaluator recommended conditions of registration including compliance with certified product details and batch release assessment (see *Quality findings* above).

Nonclinical

The nonclinical dossier was in accordance with the relevant ICH guideline for the nonclinical assessment of biological medicines. The pivotal safety-related studies were GLP compliant and all animal studies used the clinical (IV) route of administration in rats and monkeys, as these species were pharmacologically responsive to rIX-FP.

rIX-FP had similar clotting activity to the comparator, BeneFIX, in plasma from rats, rabbits, monkeys and human. Haemostatic efficacy, comparable to that of BeneFIX, was demonstrated in appropriate mouse and dog models of haemophilia B. Prolongation of the clotting activity in dogs was correlated with a more sustained increase in plasma FIX concentration compared with that observed with BeneFIX.

The tissue distribution was comparable to that of BeneFIX, indicating that it was not altered by albumin fusion. The elimination of radioactivity was slower than that of BeneFIX, but was comparable to that observed following IV administration of radiolabelled albumin, suggesting that albumin fusion is responsible for the prolonged tissue half-life of rIX-FP.

There were no objections to registration.

Pregnancy category

The nonclinical evaluator recommended the Pregnancy category should be B2 and the sponsor has agreed to this.

Clinical

In the second round clinical evaluation, albutrepenonacog alfa was recommended for approval for the indication:

> *Idelvion is indicated for the treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency), including the peri-operative setting. Idelvion can be used in all age groups.*

The Indication proposed by the sponsor at submission and following the second round evaluation was

Idelvion is indicated in all patients with haemophilia B for:

- *Routine prophylaxis to prevent or reduce the frequency of bleeding episodes*
- *Control and prevention of bleeding episodes*
- *Control and prevention of bleeding in the perioperative setting.*

The clinical evaluator concluded that Study 3001 demonstrated efficacy and safety of rIX-FP in previously-treated adults and adolescents; switching from on-demand regimen to prophylaxis showed reduction in spontaneous and total haemorrhages, and bleeding could be managed with 1 or 2 infusions. Similarly in Study 3002 paediatric subjects < 12 years using a 7 day dosage interval for prophylaxis had low rates of haemorrhage, and treatment of bleeding episodes with rIX-FP was effective. Surgery data were considered adequate on receipt of additional information.

In the first round evaluation, the evaluator did not agree with the dosage regimens initially proposed, because the wording implied that either 7 day or 14 day intervals could be chosen at initiation. This did not reflect clinical trial data provided: adults and adolescents were selected for 14 day dosing regimens only if well controlled using up to 40 IU/kg on the 7 day regime, and no children < 12 years were treated with 14 day regimens.

The sponsor subsequently modified the dosage regimens proposed recommending selection of patients for extended regimens.

Overview of data

Clinical Studies 2001, 2004, 3001 and 3002 were open label trials in previously treated males with severe haemophilia, providing PK, efficacy and safety data. Subsets of these patients had comparable PK measurements obtained for previously used FIX replacement. There was one population PK analysis that used data from these trials.

Study 3003 is an ongoing Phase III efficacy and safety trial; it is the only study to enrol previously untreated patients (PUPs), so completed pre-registration data for this group are lacking.

This stepwise approach to clinical development is in line with EU guidelines for recombinant products for treatment of haemophilia B.

Formulation

Drug product from the Pilot Scale Process was used in clinical Studies 2001 and 2004. Drug product from the Commercial Scale Process was used in Phase III studies (3001, 3002 and 3003). No changes were made to the active ingredient or excipients.

Pharmacology

rIX –FP is administered intravenously. Factor IX activity is measured in individual plasma samples by in vitro aPTT ‘one-stage clotting assays’. 1 IU/dL equates to 1% FIX activity.

Incremental recovery (IR) is the maximum (peak) FIX activity (IU/dL) obtained through 30 minutes following injection, per dose (IU/kg) of injection. The evaluator considered that the study designs, conduct and analyses were satisfactory.

In adults and adolescents of 12-18 years (Study 3001), mean IR (CV%) after a single dose of 50 IU/kg was 1.31 (23.5) IU/dL per IU/kg, higher than for previously-used recombinant FIX and comparable to plasma-derived FIX (0.961 (27.2) and 1.30(25.7) IU/dL per IU/kg respectively).

In pooled PK data for adults ≥ 18 years (n = 47) following a single dose of 50 IU/kg, IR (CV%) was 1.30 (23.8) compared to previous FIX product 1.00 (25.7).

In children (n = 27) aged < 12 years (Study 3002) mean IR IU/dL per IU/kg (CV%) was 1.01(22.5) (< 6 years 0.951, 6-<12 years 1.06) compared to previous FIX (n = 17) IR 0.738 (26.8). PK parameters for different age groups following single injection of 50 IU/kg are proposed for inclusion in the PI.

In all age groups C_{max} and AUC were higher after rIX-FP than previous FIX. There was no clinically significant change in PK of rIX-FP as measured in 15 subjects after 6 months of prophylaxis treatment.

Clearance was higher in children; mean 1.11 mL/h per kg, compared to 0.75 mL/hr per kg in adults and adolescents (about 0.875 mL/h for a 70 kg individual). In all age groups mean clearance was lower than for previously used FIX products. Half-life in adults and adolescents was 90 to 100 h; in children mean half-life was about 91 h.

Population PK

Using final FIX activity population PK model for simulations, the model predicted that the median for trough FIX activity would be maintained at > 1% at dosage intervals of 7 days (25 or 40 IU/kg) or 14 days (50 or 75 IU/kg). The clinical evaluator noted that in PK modelling for 14 day intervals in children < 6 years at a dose of 50 IU/kg, median trough FIX levels approached 1%. These estimates suggested that in a significant proportion of young children FIX would fall below 1% and might require shorter intervals or higher dosing.

In response to the first round clinical evaluation, the sponsor referred again to modelling predicting that for a dose of 75 IU/kg with a 14 day interval, 75% of patients < 6 years of age would have a trough level above 1.1%; conversely it appears the modelling suggests 25% would have a trough level below 1.1%.

Delegate's Conclusion: Pharmacokinetics

The PK of rIX-FP has been adequately characterised within the requirements of relevant EU Guidelines. Administration was associated with restoration of FIX activity in subjects with severe FIX deficiency. FIX activity was prolonged and IR higher compared to recombinant and plasma-derived FIX replacement products previously used by the subjects in the studies provided. However, children have increased clearance and higher volume of distribution compared to adults and this was associated with lower plasma FIX activity levels.

Drug-drug interactions

No data was submitted.

Efficacy

Bleeding episodes were assessed in Studies 2001, 3001, 3002 and the surgery substudy of 3003.

Study 3001

This was a Phase III open label 2-arm study in previously treated patients aged 12 to 65 years with severe haemophilia B. The primary efficacy objective was to evaluate the efficacy of rIX-FP in preventing bleeding episodes when administered as routine prophylaxis. Secondary efficacy objectives included evaluation of the clinical response to rIX-FP when administered on-demand for the treatment of bleeding episodes and efficacy of rIX-FP when administered as surgical prophylaxis.

Inclusion and exclusion criteria included severe haemophilia B, aged 12 to 65 years, previously treated for > 150 exposure days (EDs) with no evidence of inhibitor formation. These criteria were consistent with EMA guidelines for studies in previously treated patients.

Randomisation and interventions

This was a non-randomised study; with patients allocated to either prophylaxis (Arm 1) or on-demand (Arm 2) treatment with rFIX-FP, based on current treatment regimens at enrolment. After 26 weeks or 12 spontaneous bleeding episodes, on-demand subjects in Arm 2 could switch to prophylaxis, commencing with 35-50 IU/kg every 7 days; the dose could be increased during the first 4 weeks up to a maximum of 75 IU/kg every 7 days.

Following prophylaxis for 26 or 30 weeks selected patients in Arm 1 could switch to a 75 IU/kg dose at 10 or 14 day interval regimen if they met the following criteria: no dose adjustment in the previous month; currently on weekly prophylaxis of ≤ 50 IU/kg; willing to switch to a longer treatment interval. The interval was 10 days if the current weekly dose was > 40 to ≤50 IU/kg, 14 days if ≤ 40 IU/kg.

Demographic and baseline characteristics

In total, 63 male subjects were treated, 40 in the prophylaxis arm (Arm 1; 37 completed) and 23 in the on-demand arm (Arm 2; 18 completed); 4 were analysed for the surgical sub-study.

Efficacy assessment methodology

The main efficacy variables were the number of bleeding episodes, (annualised bleeding rate =bleeding episodes/year/subject), amount of FIX-FP used for on-demand and prophylactic treatment, and investigator's overall assessment of efficacy. The pre-specified primary efficacy endpoint was the annualised spontaneous bleeding rate (AsBR) in the on-demand treatment arm (Arm 2).

Efficacy outcomes

See Attachment 2 for more details.

Bleeding episodes

Primary efficacy endpoint Mean (SD) annualised spontaneous bleeding rate (AsBR) in 19 subjects in Arm 2 was 14.6 (8.42) while receiving on-demand treatment, and 0.73 (1.17) when receiving a prophylaxis regimen, a mean reduction (SD) of 96% (5.54), p< 0.0001.

Total bleeding episodes expressed as mean annualised bleeding rate (ABR) was 20.28 during on-demand treatment and 2.87 on the prophylaxis regimen. In 98.6% of the total 358 bleeding episodes, haemostasis was achieved with 1 or 2 infusions, similar for all types of bleeding episodes.

For prophylaxis, AsBR mean (SD) for 7 day intervals was 0.23 (0.911) vs. extended regimens of 10 –day or 14 day intervals 0.85 (1.921), a mean difference (95% CI) -0.62 (-1.411 to + 0.163).

This matched-pairs analysis on 26 subjects from Arm 1 who received at least 12 weeks of treatment with two regimens met pre-defined criteria for non-inferiority.

Investigator's assessment of efficacy response was excellent or good for 94.2% of episodes, and moderate in 2.5%; the single 'poor/no response' report occurred with a single dose of 39.37 IU/kg; on this occasion a second dose was not administered when the bleed was not adequately treated by the first dose.

Study 3002

This was a Phase III open label, single arm study in previously treated paediatric patients, < 12 years, with severe haemophilia B. The study took place in 10 countries including Australia, January 2013 to October 2014. After initial screening, there was a 14 day PK evaluation of a single dose of 50 IU/kg of rIX-FP. The active treatment was weekly prophylaxis therapy with rIX-FP for approximately 11 months. The primary objectives were to assess PK and safety with respect to inhibitor development; secondary objectives were assessments of safety based on AEs, and clinical response for prevention and treatment of bleeding episodes.

Inclusion and exclusion criteria

The study enrolled previously treated males younger than 12 years of age with FIX activity ≤ 2%, and no FIX inhibitor formation. The evaluator noted that criteria were generally consistent with the EU Guideline.

Interventions

All patients initially received a single dose of 50 IU/kg rIX-FP for PK assessment. A subset had PK assessment of the previously-used FIX product, prior to administration of rIX-FP.

For prophylaxis, subjects were initially treated with 35-50 IU/kg rIX-FP every 7 days. This could be increased by an increment of 5 to 15 IU/kg, to a maximum of 75 IU/kg, with a target of maintaining trough activity FIX level above 3% to 5%.

The 7 day dosage interval was maintained throughout the study.

For treatment of haemorrhages the initial dose was 35 to 50 IU/kg rIX-FP. If haemostasis was not achieved the caregiver was to contact the study centre for instruction. If a maintenance dose for treatment of haemorrhage was required, the second dose 24 h later followed testing of FIX activity level. The dose could be increased up to 75 IU/kg for subsequent haemorrhages. The prophylaxis schedule was to resume 7 days after the last dose used for treating the bleeding episode.

For surgical procedures, the aim was to increase plasma FIX activity levels to 60 to 80%.

Demographic and baseline characteristics

In total, 27 male subjects were enrolled, with mean age of 5.9 years, range 1-10 years; 12 of them were < 6 years; most had been on prophylaxis with a recombinant product and 2 of them underwent surgery. The sample size was consistent with guideline recommendations.

Efficacy assessment methodology

All efficacy measures were considered secondary or 'other' endpoints. Efficacy variables included the number of bleeding episodes, amount of FIX-FP used for on-demand and prophylactic treatment, investigator's overall assessment of efficacy, and proportion of bleeding episodes requiring 1, 2 or > 2 infusions of rIX -FP.

Efficacy outcomes

See Attachment 2 for more details.

Bleeding episodes

There were 126 bleeding episodes in total, 106 of which required treatment, 94 with 1 infusion only. There were 3 bleeds that required > 2 infusions. All were joint haemorrhages, 2 being traumatic and 1 spontaneous. They were each treated with 3 or 4 infusions. In each instance there was some delay in initiation of treatment.

The median dose per infusion was approximately 46 IU/kg; consumption was slightly greater in children < 6 years.

Investigator's assessment of efficacy was excellent or good for 96.2% of mild/moderate bleeding episodes, and good for 2 reported major traumatic hip joint bleeds, in one child < 6 years.

For total bleeding episodes, the mean (SD) annualised bleeding rate (bleeding episodes per/year/subject) was 4.22(3.561) for children below 6 years (n =12) and 3.44(3.178) for children aged 6 to < 12 years.

Mean spontaneous bleeding rate (AsBR) for the entire group (n=27) was 0.57, with 1/12 children < 6 years and 9/15 aged 6 to <12 years requiring treatment for at least 1 spontaneous bleeding episode. Joint bleeding episodes requiring treatment occurred in 6/12 children below 6 years and 10/15 aged 6 to < 12 years.

Other studies

Study 2004

Following PK assessment, there was a 20 week treatment period of prophylaxis (15 to 35 IU/kg weekly based on PK profile, adjusted up to 75 IU/kg weekly to maintain FIX trough levels > 1%, n = 13) or on-demand treatment as decided by investigator (n =4). Age range was 13 to 46, mean 26.1 years. Results were consistent with pivotal studies; mean of bleeding episodes in the last 12 weeks of treatment was 0.8 in the prophylaxis group versus 6.8 in the on-demand group.

Study 3003

This open label Phase IIIb trial is ongoing; the primary objective is safety evaluation. Efficacy data were provided in the original submission as interim analyses from the surgery sub-study only, for 7 subjects undergoing surgery; mean pre-operative dose was 79 IU/kg, with total doses 3-7.

In the sponsor response to clinical evaluator's recommendations to the PI, the sponsor acknowledged that the 14 day interval for prophylaxis had not been tested in paediatric study 3002. The final median dose in Study 3002 was 50 IU/kg (n = 27).

The sponsor provided additional data from 24 children enrolled in Study 3003 after completion of 3002. Of these 24 children, 11 were switched to an extended treatment interval; 6 were stated to be on a 14 day interval as at the 28 July 2015 cut-off date for Study 3003. The sponsor provided a summary of bleeding rates for subjects < 12 years of age to support the claim that paediatric subjects experienced similar bleeding rates on weekly and extended regimens and the proposed dosage interval up to 14 days at a dose of 75 IU/kg in some children. The median (SD) ABR was 3.8(3.31) for the 7 day interval in 3002 (n = 27) and 3.1(3.02) for the available information for the 14 day interval in 3003 (n = 6).

It is noted that the numbers for the new data are small, the study has not been fully evaluated (only the surgical sub-study was discussed by the evaluator) and this study is not scheduled for completion until 'approximately 2018'.

Delegate's conclusion regarding efficacy

Efficacy has been adequately demonstrated for Albutrepenonacog alfa (Idelvion) for the indication proposed for the sponsor but the data are insufficient at present to support extended treatment intervals for prophylaxis regimens in children under 12 years of age.

Safety

A pooled analysis of safety data from Studies 2001, 2004, 3001 and 3004 was provided. Safety data from ongoing Study 3003 was presented separately. Overall, adverse events in the pooled data were as expected for the patient population. Two discontinuations for AEs were for headaches and hypersensitivity.

Exposure

In the pooled safety population there were 107 unique subjects; median for exposure days was 63, median for on study was 469. Exposure matched or exceeded the guideline requirements of at least 40 subjects with >50 EDs, including 10 aged < 6 years and 10 aged 6-< 12 years; actual number were 75, 10, and 15 respectively.

Study 3003

There were safety data provided for 4 new patients, and 76 from earlier studies.

Hypersensitivity

A 22 year old subject had a hypersensitivity event during the fourth infusion of rIX-FP and he discontinued treatment. Immunogenicity testing conducted approximately 3 weeks later was negative for FIX inhibitors and antibodies to rIX-FP.

Immunogenic events and inhibitor formation

No treatment-emergent antibodies to rIX-FP or CHO were detected in submitted studies in the dossier originally submitted for evaluation. No inhibitors against FIX were reported in the studies that enrolled previously-treated patients with no personal or family history of inhibitors, that is low-risk of developing inhibitors. The clinical evaluator noted rFIX-FP is a novel molecule and potentially may be more antigenic than plasma derived or recombinant FIX.

The sponsor subsequently provided additional information for 3 previously untreated patients (PUPs) enrolled in 3003. Two were described as 'not dosing' as of the data cut at 28 July 2015. The other was a subject who developed a mild allergic reaction associated with FIX in July 2015 after 13 exposure days to 50 IU/kg rIX-FP/week. He was switched to on-demand dosing with 100 IU/kg with pre-treatment oral cetrizine; 4 bleeding episodes up to March 2016 have been thus treated. Genetic testing detected a large deletion including exons 7 and 8 of the Factor IX gene, consistent with a higher risk of inhibitor development.

Subsequently an additional PUP started 50 IU/kg weekly in August 2015 with no hypersensitivity or inhibitor development reported.

Delegate's conclusion regarding safety

The safety profile for albutrepenonacog alfa as described in the clinical studies provided is similar to other comparable products and is acceptable.

One of four previously untreated patients has developed FIX inhibitor. Idelvion is a novel molecule and potentially may be more antigenic than plasma derived or recombinant FIX Adverse events of hypersensitivity and a statement about inhibitor development in PUPs have been added to the proposed PI.

Updated information on safety in PUPs is expected with the sponsor's pre Advisory Committee on Prescription Medicines (ACPM) response.

Risk management plan

The updated EU RMP was acceptable. The ASA included effects on fertility and experience with long-term use as missing information and Study 3003 was added to the Pharmacovigilance plan. Other issues raised were resolved by additions to the PI, with the exception of including risk factors for inhibitor formation. The sponsor stated that such risk factors were not confirmed for Haemophilia B and that the proposed PI contained information consistent with other marketed products.

Recommended conditions of registration

The suggested wording is '*Implement EU-RMP Version 2.0 (dated 29 January 2016, DLP 9 January 2015) and Australian-specific annex (ASA) Version 2.0 (dated 29 March 2016) and future updates where TGA approved, as a condition of registration*.'

Risk-benefit analysis

Delegate's considerations

Efficacy

1. Extended treatment intervals for prophylaxis dosage regimen

The claim that for prophylaxis the increased interval to 14 days can be used for some paediatric patients is based on PK modelling and limited efficacy data from the incomplete Study 3003. It is proposed by the sponsor that the risk of inadequate FIX replacement would be managed by restricting the option to those children who have been stable and well controlled using the 7 day interval.

It is acknowledged that haemophilia management requires close monitoring as well as individual treatment adjustments based on clinical context including age, disease severity, and FIX level. It is also acknowledged that fewer injections are desirable, particularly in younger age groups.

- However the Delegate has concerns that data are insufficient to justify the recommendation for extended intervals in the younger age groups.
- It is noted that this increased interval has not been recommended in the US PI and European Summary of Product Characteristics (SmPC), although the latter mentions ongoing trials in this area.

2. Monitoring

For this novel product, there appears to be some uncertainty around aPTT tests using available laboratory test kits, and clinical interpretation. The PI should clarify this issue.

- The Delegate proposes an additional sentence stating patients should be monitored for adequate Factor IX activity levels at the beginning of the Precautions section. As described in Dosage and Administration and clinical practice guidelines for recombinant FIX, this is part of standard clinical monitoring.
- The 'Effect on laboratory tests' paragraph should include information relating to the specific product interaction of Idelvion with aPTT testing, and any other effects on laboratory testing.

Safety

Hypersensitivity and inhibitor formation are documented adverse events with FIX replacement therapies. Additional data are required to clarify the degree of immunogenicity in this new product, particularly in previously untreated patients.

- The lack of data in the previously untreated patient group should be emphasised in the PI by including an additional sentence under Precautions.
- Should albutrepenonacog demonstrate greater immunogenicity and/or risk of inhibitor formation than other products this would prompt review of the risk/benefit profile.

Planned or ongoing studies

Study 3003 is ongoing; there appear to be no other planned studies.

- Conditions of registration should include provision of full study reports to TGA as available.

Overall risk-benefit analysis and indication

The benefit expected with albutrepenonacog alfa is prevention and treatment of bleeding in haemophilia B. Dosage is individualised based on patient characteristics and response and treatment intervals of 7 days for prophylaxis regimens can be recommended.

Albutrepenonacog alfa is a new molecule and data are lacking for previously untreated patients. Risks associated with the potential for thrombotic complications and FIX inhibitors would be monitored and managed as for other FIX replacement therapies.

Given the proposed usage the Delegate considers the overall risk-benefit is positive for the Indication:

Idelvion is indicated in all patients with haemophilia B for:

- *Routine prophylaxis to prevent or reduce the frequency of bleeding episodes*
- *Control and prevention of bleeding episodes*
- *Control and prevention of bleeding in the perioperative setting.*

However issues not yet fully resolved include advice about assays for monitoring of FIX levels in clinical practice, and dosage for prophylaxis in the paediatric age groups.

Questions to sponsor

1. The sponsor should provide details about estimation of FIX activity for albutrepenonacog alfa in tests commonly utilised in the Australian clinical setting, and any potential influence on management. It is noted that in the USA, the sponsor has agreed to send a DHCP letter and provide support for questions about laboratory monitoring.
2. The sponsor should clarify the status of new information from Study 3003; were the data provided in response to the Round 2 evaluation part of a planned interim analysis?
3. Please provide any available updated safety information, with specific reference to immunogenicity, in the pre-ACPM response.

Proposed action

The Delegate had no reason to say, at this time, that the application for albutrepenonacog alfa (Idelvion) should not be approved for registration.

Request for ACPM advice

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

- Are the proposed dosing instructions for prophylaxis for children <12 years of age acceptable, or is the wording in the European Summary of Product Characteristics more appropriate?
- Is the proposed information on monitoring laboratory tests adequate?

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

Response from sponsor

Questions to sponsor

Question 1

The sponsor should provide details about estimation of FIX activity for albutrepenonacog alfa in tests commonly utilised in the Australian clinical setting, and any potential influence on management. It is noted that in the USA, the sponsor has agreed to send a DHCP letter and provide support for questions about laboratory monitoring.

Response

Globally, FIX activity is routinely monitored using the one-stage clotting assay and this assay is recommended in the product labelling for Idelvion. It is widely accepted that there can be a variance in the FIX activity results depending on the aPTT reagent used in the assay and this has been confirmed by a recently published field study conducted by the NIBSC.[22]

The sponsor has investigated the impact of 9 different aPTT reagents used in the one-stage clotting assay and the results showed that activity can be underestimated by 50% when 2 of these reagents, Actin FS and Kaolin based aPTT reagents, are used. The other 7 reagents delivered comparable results.

Following consultation with Australian laboratories involved in FIX activity testing, the sponsor confirms that Kaolin based aPTT reagents are not used and whilst the use of Actin FS cannot be completely excluded, its use is highly unlikely.

In response to this questions and to appropriately address this monitoring concern, the relevant section of the Australian PI (Monitoring Laboratory Tests) has been revised and expanded and is now consistent with the EU SPC and US PI.

Finally, please note that the Dear Health care Provider (DHCP) letter issued in the USA was requested by FDA to address the class safety concern with variability in the assays used during treatment monitoring of FIX levels and there are no concerns specific to Idelvion.

[22] Wilmot HV et al. Recombinant factor IX: discrepancies between one-stage clotting and chromogenic assays. Haemophilia 20(6):891-897

Question 2

The sponsor should clarify the status of new information from Study 3003; were the data provided in response to the second round evaluation part of a planned interim analysis?

Response

An abbreviated Clinical Study Report (Version 1.0, 24 February 2015) for the surgery data of Study 3003 was submitted in the initial application for Idelvion. This included 80 subjects with an overall mean time on study of 6.78 months.

The additional data from Study 3003 (28 July 2015 data-cut) provided in response to Clinical question 9 was not part of a planned interim analysis. Whilst the protocol does not plan for an interim analysis (for either safety of futility evaluation) it does allow for the possibility of providing efficacy, safety or PK data to address any concerns raised by Health Authorities (HA). Given that the study is an unblinded, open label study, a negative impact on data integrity is neither expected nor plausible.

The 28 July, 2015 data-cut was intentional in order to support on-going safety evaluation for Idelvion and preparation of the Development Safety Update report (DSUR) for markets that require this data to be formally submitted . At this time, the sponsor also conducted an ad hoc analysis from efficacy data available at this data point, as it coincided with questions received during the EMA MAA evaluation. The efficacy tables from this analysis were provided to TGA to further support the 14 day prophylaxis interval.

Question 3

Please provide any available updated safety information, with specific reference to immunogenicity, in the pre-ACPM response.

Response

The data from the 28 July 2015 data cut (that supported the 2015 DSUR safety analysis) is the most current safety information available and the next safety analysis for Study 3003 is planned for 28 July 2016 (and will support preparation of the 2016 DSUR). However, there are several adverse events (AEs) that are monitored as AE of special interest (AESIs) to enable an adequate risk-benefit evaluation of Idelvion versus standard therapy during the study. All AESIs are considered medically significant and are therefore Serious AE (SAEs) and undergo expedited reporting procedures as outlined in ICH Topic E2A.[23] The AESIs include:

- AEs associated with confirmed (that is, with second blood sample) inhibitor formation
- Thrombotic and/or embolic events
- Anaphylaxis

The sponsor can confirm that as of the 7 July 2016, no previously treated patient (PTP) had developed an inhibitor to Idelvion. In regard to previously untreated patients, (PUPs) there are 4 currently enrolled in the extension study and 2 were treated with Idelvion. Besides the PUP inhibitor case that was included in the sponsor's response (and the updated Risk Management Plan (RMP)/Australian Specific Annex (ASA)), no new inhibitor case or anaphylaxis case has been reported from the ongoing 3003 study.

Other than this inhibitor case, there were no other related SAE cases identified between 29 July, 2015 and 7 July, 2016. Ongoing monitoring of study subjects and routine signal detection activities has not identified new safety concerns. The sponsor will continue to

[23] Clinical safety data management: definitions and standards for expedited reporting E2A

provide up to date safety information for Idelvion following approval in the form of Periodic Safety Update Reports (PSURs).

Response to recommended changes to the PI

Pharmacology Paediatric population

The statement requested by the Delegate has been included in the PI and repositioned as requested.

Please note that information on the predicted times from the Population PK (Pop PK) analysis at the 75 IU/kg dose have also been added to the PI and the paragraph referring to time to 1% FIX activity has been retained as this information is still considered relevant and important for health care providers (HCP) to make an informed judgement for dosing on an individual patient basis.

Clinical trials

The statement requested by the Delegate has been included in the PI, with amendments. These amendments have been made to ensure the statement is factually correct and the HCPs are provided relevant information. The amendments include retaining the information on the number of subjects on a prophylactic treatment regimen that were switched to an extended dose interval, maintaining the reference to the 50 IU/kg dose and adding detail to the switching criteria for completeness.

Precautions

The Delegate requested the inclusion of an additional sub-heading in the PI with regard to 'Monitoring'. Instead of creating this additional sub-heading and having HCPs referring to multiple locations for this information, the 'Monitoring laboratory tests' section has been relocated to the beginning of the 'Precautions' section.

The Delegate has also referenced an 'Effect on laboratory tests' section, however, it should be noted that in the Australian PI this section is referred to as 'Monitoring laboratory tests' and contains the expected and relevant information. Please refer to response to Question 1 above, for further information on monitoring.

The statement requested by the Delegate with regard to PUPs has been included in the 'Precautions' section.

Dosage and Administration

The sponsor has retained the current paediatric prophylaxis wording that includes the 14 day dosing regimen. Please refer to the section 'Other issues identified in Request for ACPM Advice' for further information.

Other printed material amendments

- The Pregnancy category B2 has been added to the PI as requested.
- The CSL NZ medical enquiries contact number has been corrected.
- No changes have been made to the CMI as a result of this evaluation and responses. The sponsor commits to maintain the alignment between CMI and PI as appropriate.

Other Issues Identified in Request for ACPM Advice

The Delegate's provide a balanced assessment of the evaluation for Idelvion, with no concerns in relation to on-demand treatment, or prophylaxis with a 7 day dose interval, in adults, adolescents and paediatrics.

The Delegate raised some concern in relation to efficacy with regard to longer dose intervals for paediatric patients on a prophylaxis treatment regimen, monitoring, safety (immunogenicity) and the status and commitment in regard to the on-going studies.

The sponsor has responded to the concerns regarding monitoring and safety (immunogenicity) in Questions 1 and 3 above and provides further comment on efficacy with regard to longer dose intervals for paediatric patients on a prophylaxis treatment regimen and the commitment regarding the on-going studies below.

Efficacy Extended treatment intervals for prophylaxis

The Delegate has acknowledged that haemophilia management requires close monitoring and individual treatment adjustment based on clinical context including age, disease severity and FIX level. It was also acknowledged that fewer injections are desirable particularly in younger age groups.

Current clinical practice for treatment of paediatric subjects follows a number of practice points from the Australian Haemophilia Centre Directors' Organization (AHCDO; both current and those under consultation[24]), Guidelines for the management of haemophilia in Australia, which include bleeding phenotype, venous access, pharmacokinetics (PK) and the activity level of patients. In Australia, haemophilia is managed by select Haemophilia Treatment Centres (HTC) and by a specific and dedicated, multi-disciplinary team and after every severe bleeding episode. At the introduction of a prophylaxis treatment regimen, PK assessment involves the establishment of trough levels for the patient so that appropriate dose for that individual maybe identified. Patients usually commence treatment with a conservative approach to dose (and dose interval), which would then be escalated to achieve a stable clinical response, control of bleeding and adequate trough FIX levels, and to then consider whether a longer dose interval is attainable based on the individual's PK.

FIX trough levels <1% are considered to indicate severe haemophilia, 1 to 5% moderate haemophilia and >5 to 40% mild haemophilia however, even patients with a mild haemophilia may bleed frequently due to the highly individualised nature of the disease. Consequently, dose investigation is essential to achieve a stable clinical and PK response and this approach is recognised by clinicians.

As acknowledged by the Delegate, there are real and tangible benefits in a longer dose interval for children, which include, but may not be limited to:

- Fewer intravenous injections and reduced risk of infection
- Reduced need for implanted central venous access device (CVAD) in young children
- Maintenance of venous access/function for a life-long disease requiring regular intravenous infusions
- Improvement in treatment compliance resulting in long term benefits such as fewer bleeding events, reduced joint damage and quality of life

For these reasons, it is appropriate and necessary to consider the suitability of longer dose intervals for paediatric patients in whom effective control of FIX levels and suppression of spontaneous bleeding has been demonstrated on the 7 day regimen.

Paediatric Dose Proposal and Supporting Data

The sponsor seeks approval for a once weekly dose schedule of 35 to 50 IU/kg (a 7 day dosing interval) and 75 IU/kg for a longer dose interval (up to 14 days) for a sub-set of paediatric patients (< 12 years of age) who are stable and well controlled on the 7 day dosing interval.

[24] http://www.ahcdo.org.au/publications/asset_id/1/cid/1/parent/0/t/publications/title/evidence-based-clinical-practice-guidelines and https://www.blood.gov.au/system/files/documents/public-consultation-draft-haemophilia-guidelines-11-nov-2015.pdf

This proposed paediatric dose is consistent with that approved in Canada, which allows a 14 day dose interval where deemed appropriate by the clinician however, EU and US have approved a maximum dose interval of 7 days for the paediatric population.

The 7 day dose interval was investigated in pivotal paediatric Study 3002 which established the efficacy of that dosage regimen. Data to support a longer dose interval was provided both in the initial submission, as a Population PK (Pop PK) modelling analysis, and in the response to a clinical question as an analysis of efficacy data from the on-going Extension Study 3003.

The Pop PK analysis included data from both pivotal Studies 3001 adults/adolescents and 3002 paediatrics (analysed as sub-groups under 6 and 6 to 12 years of age) and PK studies 2001 and 2004. Simulations for modelling included 7, 10 and 14 day dose intervals at 25, 40, 50 and 75 IU/kg.

Data from ongoing Study 3003 provided additional information on paediatric subjects on extended dosing intervals. The data showed that paediatric subjects in Study 3003 on extended dosing intervals experienced similar bleeding rates to those on weekly regimens in Study 3002.

The Pop PK modelling data is also supportive of a 14 day dose interval in children. The data presented in the Delegate's overview shows that the model examined 2 sub-groups of paediatric patients (<6 and 6 to 12 years of age) and dose intervals of 7, 10 and 14 days. The Delegate identified that for children in the < 6 years of age sub-group, 75% are predicted to have trough levels above 1.1% at a dose of 75 IU/kg, with a dose interval of 14 days and 25% may therefore have a trough levels below 1.1%. However, this sub-population is not representative of the whole paediatric population or of the whole data set which must include evaluation of the predictions for the 6 to 12 years of age sub-group.

The paediatric group as a whole is defined as 0 to 12 years, and the Pop PK modelling predicts that for children aged 6 to 12 years, at a dose of 75 IU/kg with a dose interval of 14 days, 75% would have trough levels above 2.3%, with the 90% confidence interval projecting trough levels in the range of 0.9 to 10.6%.

It is also relevant to consider the predicted duration of time, for which the median FIX level is maintained above a target trough level. The efficacy component of the prophylaxis arm of the clinical trial targeted FIX levels above 3%. This information is presented in the Delegate's Overview. The simulated duration above 3% after a single dose at 75 IU/kg is 12 days for <6 years, 15 days for 6 to 12 years and 18 days for 12 to 18 years.

Therefore, when the 2 sub-groups (<6 and 6 to <12) are considered as a whole, it is clear that a large portion of the paediatric population has the potential to benefit from effective treatment at the 14 day dose interval.

Regarding the Delegate's concern with respect to maintenance of adequate trough levels in children is well recognised by HCPs, HTCs and the sponsor. Close clinical management of these patients at the time the dose interval is extended, involves monitoring trough levels and surveillance of breakthrough bleeding events to ensure the most effective dosing regimen is provided to each patient on an individual basis.

The Australian Haemophilia Centre Directors' Organisation (AHCDO) guideline includes clinical management recommendations which have been developed and implemented by the 17 HTC across Australia; thus ensuring adherence to monitoring and maintenance of individual patients so that they are not progressed to extended dose intervals inappropriately.

The sponsor has acknowledged there is a need to ensure that the 14 day dose interval is only used in the paediatric patients in whom effective control of bleeding and stable FIX levels have been demonstrated on the 7 day regimen. The PI was amended to ensure that patients at risk are not switched to extended dose intervals by:

- Including the PK data and Pop PK modelling information in the PI which allows clinicians to individualize the appropriate regimen for any given patient
- Including information in the clinical trials section regarding the design of the trial and description of when patients were extended
- Including statements in the Dosage Section

Finally, in recent communications the sponsor has shared the paediatric clinical trial data with 2 leading Australian paediatric haematologists (Directors of HTC). These 2 clinicians have confirmed that a longer dose interval is substantially beneficial to paediatric patients, based on their experience in treating young children and that any concern regarding management of trough levels can be appropriately addressed by current clinical practices.

Whilst the sponsor recognises that the clinical trial data supporting the extended dose intervals is limited at this time, when the Pop PK modelling data are considered in conjunction with the highly individualised nature of this disease and the potential benefits for this vulnerable population, restricting the dosage recommendation to a 7 day interval in all children would reduce the options available for treating patients who are stable and well controlled.

Planned or on-going studies

The sponsor is committed to ensuring the TGA is kept abreast of new safety and efficacy data arising from on-going clinical studies.

For Idelvion, the Extension study 3003 (A Phase IIIb open-label, multicentre, safety and efficacy extension study of rIX-FP in subjects with haemophilia B) is currently ongoing. In line with the RMP, a progress study report will be submitted within 2 years after Marketing Authorisation (MA) in the EU (MA approval obtained 11 May 2016), which would also be provided to TGA, as will the final company study report (CSR).

Furthermore, safety data will be provided on a regular basis with each PSUR submitted post approval of Idelvion in Australia.

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 ACPM resolved to recommend to the TGA delegate of the Secretary that:

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Idelvion Powder for solution for injection, vials containing 250 IU (100 IU/mL when reconstituted, with water for injection provided as part of an administration pack); 500 IU (200 IU/mL); 1000 IU (400 IU/mL); 2000 IU (400 IU/mL) of albutrepenonacog alfa to have an overall positive benefit–risk profile for the sponsor's proposed indication**;**

Idelvion is indicated in all patients with haemophilia B for:

- *Routine prophylaxis to prevent or reduce the frequency of bleeding episodes*
- *Control and prevention of bleeding episodes*
- *Control and prevention of bleeding in the perioperative setting*

In making this recommendation the ACPM

- noted that albutrepenonacog alfa demonstrated reasonable efficacy for the proposed indication with no major safety issues

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 about proposed amendments to the Product Information (PI) and specifically advised the Consumer Medicine Information (CMI) should be further reviewed for clarity, and consistency with the final PI.

Negotiation of the Product Information and Consumer Medicine Information should be to the satisfaction of the TGA.

Specific Advice

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

1. *Are the proposed dosing instructions for prophylaxis for children <12 years of age acceptable, or is the wording in the European Summary of Product Characteristics more appropriate?*

The ACPM recommended that dosing for prophylaxis for children under 12 years of age should follow the 7 day interval treatment (35 to 50 IU/kg once weekly), as per the instructions on the *Posology* section of the European Summary of Product Characteristics.

It was noted that clinical studies are on-going in this patient group, investigating safety and efficacy and longer treatment intervals than once weekly. A statement about flexibility of dosing with close monitoring by specialist physician may be considered.

2. *Is the proposed information on monitoring laboratory tests adequate?*

The ACPM noted that the information on monitoring laboratory tests is relevant and consistent with current clinical practice. No amendments are required.

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

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

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Idelvion [albutrepenonacog alfa (recombinant fusion (FP) linking coagulation factor IX with albumin)] 250 IU, 500 IU, 1000 IU, and 2000 IU powder for Injection.

The approved indications for these therapeutic goods are:

Routine prophylaxis to prevent or reduce the frequency of bleeding episodes

Control and prevention of bleeding episodes

Control and prevention of bleeding in the perioperative setting.

Specific conditions of registration applying to these goods

- The Idelvion EU-Risk Management Plan (RMP), version 2.0, dated 29 January 2016, DLP 6Ianuary 2015), and Australia Specific Annex (AsA) Version 2.0 (dated 29 March 2016), and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

· Batch release testing:

a. It is a condition of registration that all batches of Idelvion rIX-FP [albutrepenonacog alfa] imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

b. It is a condition of registration that each batch of Idelvion rIX-FP [albutrepenonacog alfa] imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch.

The sponsor must supply:

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

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

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

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

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

Attachment 1. Product Information

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

Attachment 2. Extract from the Clinical Evaluation Report

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