EMA/562322/2020
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Alprolix

International non-proprietary name: eftrenonacog alfa

Procedure No. EMEA/H/C/004142/II/0029

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

The PRAC/CHMP Rapporteurs should complete the 'actual' date at each stage of the procedure. This is the date of circulation of the report to CHMP/PRAC members.

Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion[2]**
☐	Start of procedure	18 Apr 2020	18 Apr 2020	☐
☐	CHMP Rapporteur Assessment Report	18 May 2020	18 May 2020	☐
☐	PRAC Rapporteur Assessment Report	25 May 2020	18 May 2020	☐
☐	PRAC members comments	29 May 2020	29 May 2020	☐
☐	Updated PRAC Rapporteur Assessment Report	02 Jun 2020	02 Jun 2020	☐
☐	CHMP members comments	02 Jun 2020	02 Jun 2020	☐
☐	Updated CHMP Rapporteur Assessment Report	04 Jun 2020	04 Jun 2020	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	09 Jun 2020	09 Jun 2020	☐
☐	Start of written procedure	09 Jun 2020	09 Jun 2020	☐
☐	Request for Supplementary Information	11 Jun 2020	11 Jun 2020	☐
☐	Re-start of procedure	08 Jul 2020	08 Jul 2020	☐
☐	CHMP Rapporteur Assessment Report	10 Aug 2020	10 Aug 2020	☐
☐	PRAC Rapporteur Assessment Report	17 Aug 2020	17 Aug 2020	☐
☐	PRAC members comments	21 Aug 2020	21 Aug 2020	☐
☐	Updated PRAC Rapporteur Assessment Report	25 Aug 2020	25 Aug 2020	☐
☐	CHMP members comments	24 Aug 2020	24 Aug 2020	☐
☐	Updated CHMP Rapporteur Assessment Report	27 Aug 2020	26 Aug 2020	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	01 Sep 2020	01 Sep 2020	☐
☐	Start of written procedure	01 Sep 2020	01 Sep 2020	☐
☒	Opinion	03 Sep 2020	03 Sep 2020	☐

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Swedish Orphan Biovitrum AB (publ) submitted to the European Medicines Agency on 8 April 2020 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Submission of a variation to update sections 4.2, 4.8 and 5.1 of the SmPC to add information on Previously Untreated Patients (PUPs) following the completion of the clinical study 998HB303 from the agreed Paediatric Investigation Plan (PIP) P/0071/2020 which was already assessed in EMEA/H/C/004142/P46 006. The PL and RMP have been updated accordingly.

Information on paediatric requirements

The application included (an) EMA Decision(s) P/0071/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0071/2020 was completed.

The PDCO issued an opinion on compliance for the PIP P/0071/2020.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

2. Overall conclusion and impact on the benefit/risk balance

The MAH requests changes in the SmPC & PL due to new clinical data obtained in previously untreated patients (PUPs) with severe haemophilia B treated with Alprolix (study 998HB303: a completed Phase III study in 33 PUPs receiving Alprolix). Proposed changes affect SmPC sections 4.2, 4.8 and 5.1 as well as PL section 4 to incorporate paediatric PUP data.

The MAH had initially provided a tabulated list of adverse reactions showing separate frequencies for PTPs and PUPs in SmPC section 4.8. As the differentiation between PTPs and PUPs is only based on their different risk for inhibitor formation, deriving frequencies of adverse reactions from pooled safety data is considered more informative. Therefore, the MAH had been asked to amend the table and corresponding text passages by calculated frequencies for all adverse reactions (except FIX inhibition and hypersensitivity) based on all treated subjects (PTPs + PUPs). The MAH did not provide the requested pooled analysis. From the data provided by the MAH, a pooled analysis is not expected to result in changes in frequency categories apart from injection site erythema (which would be changed from "common" to "uncommon"). The MAH was advised that omission of a pooled analysis can eventually be accepted since the presented frequency category rather overestimates the frequency which can be considered a more conservative approach. Nevertheless, data presentation in section 4.8 needed some further revision, namely the deletion of footnotes indicating differences between PTPs and PUPs apart from FIX inhibition and hypersensitivity. This was revised accordingly after the second round of assessment.

While reporting frequencies of FIX inhibition and hypersensitivity only in PUPs is considered adequate, the MAH specified upon request that both events occurred in a single previously untreated patient and that frequency calculations are not based on the entire population of treated subjects. This is endorsed.

Importantly, the MAH recently submitted study 998HB303 in accordance with article 46 of regulation (EC) No 1901/2006. This procedure (EMEA/H/C/004142/P46 006) is completed with a positive outcome with this type II variation.

As part of the article 46 procedure clarifications on several aspects had been requested with relevance also to the current variation request. Issues mainly pertaining to a considerable high number of subjects who did not complete the visits for inhibitor testing, a discussion of the impact on inhibitor detection (which might have impacted on the reported frequencies), clarifications on several efficacy related issues, (e.g. high numbers of injections needed to resolve bleeds in 2 patients, lack of haemostatic efficacy data for a high number of injections) have by now all been adequately addressed.

Therefore, no outstanding issues on safety or efficacy remain.

3. Recommendations

Based on the review of the submitted data, this application regarding the following change:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Submission of a variation to update sections 4.2, 4.8 and 5.1 of the SmPC to add information on Previously Untreated Patients (PUPs) following the completion of the clinical study 998HB303 from the agreed Paediatric Investigation Plan (PIP) P/0071/2020 which was already assessed in EMEA/H/C/004142/P46 006. The PL and RMP have been updated accordingly.

☒ is approvable

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0071/2020 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Update of sections 4.2, 4.8 and 5.1 of the SmPC as well as section 4 of the Package Leaflet to include paediatric data on Previously Untreated Patients (PUPs) following the completion of a phase III study 998HB303.

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

Recombinant factor IX Fc fusion protein (rFIXFc, Alprolix) is a long-acting, fully recombinant coagulation factor IX Fc fusion protein consisting of human coagulation factor IX (FIX) covalently linked to the Fc domain of human immunoglobulin G1 (IgG1).

rFIXFc acts by temporarily replacing the missing endogenous FIX needed for effective hemostasis in people with hemophilia B. While the FIX moiety of rFIXFc retains FIX coagulation activity, the Fc component of rFIXFc binds to the neonatal Fc receptor, thereby increasing plasma-half life (protection from lysosomal degradation).

Alprolix is approved for treatment and prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency) in all age groups.

The SmPC and leaflet changes proposed in this variation are based on results from the clinical study 998HB303: An Open-Label, Multicenter Evaluation of the Safety and Efficacy of Recombinant Coagulation Factor IX Fc Fusion Protein (rFIXFc; BIIB029) in the Prevention and Treatment of Bleeding in Previously Untreated Patients With Severe Hemophilia B. The clinical study report was already submitted on 18 February 2020 (EMEA/H/C/004142/P46 006) to meet the requirement to provide paediatric data within 6 months of End of Study. At the time of the first assessment of this type II variation, the P46 procedure was in the clockstop phase awaiting additional clarification by the MAH.

During the P46 assessment, it was concluded that safety and tolerability of Alprolix in PUPs appear largely comparable with the data generated in previously treated patients. Several uncertainties including FIX inhibitor development and efficacy outcomes needed to be clarified by the MAH as outlined in the assessment report of the P46 procedure. Therefore, no final conclusions on the requested SmPC changes could be made at that point. With this variation, all requests for additional clarification raised during the P46 procedure were addressed satisfactorily.

6. Risk management plan

The MAH submitted an updated RMP version with this application. The (main) proposed RMP changes were the following:

Summary of significant changes in this RMP:

- Part II: Revision of the safety specification to reflect cumulative post-marketing experience and completion of Study 998HB303 in previously untreated patients, and to the GVP Module V Rev. 2, as applicable.
- Part III: Removal of study 998HB303 provisions, as study is completed.
- Part V and VI: Updated to reflect changes in Part II and III.

1. Updated version Part II: Module SIII-Clinical trial exposure

From 27 April 2010 (the Developmental International Birth Date) through 04 October 2019, 186 subjects have been enrolled and dosed with rFIXFc in the Biogen/ Bioverativ/ Sanofi-sponsored clinical studies. The cumulative subject exposure from completed clinical studies, is shown by age range and racial group in the table below:

Table 1 (table 2 from RMP): Subjects Exposed in rFIXFc Clinical Studies by Age and Racial group as of 04 October 2019

	Completed Studies in PTPs			Completed Study in PUPs	
Age (years)[a]	**998HB102 (N = 123)**	**9HB02PED (N = 30)**	**9HB01EXT (N = 120)**	**998HB303 (N = 33)[b]**	**Total (N = 186)**
<6	0	15 (50.0%)	13 (10.8%)	33 (100.0%)	48 (25.8%)
6-11	0	15 (50.0%)	14 (11.7%)	0	15 (8.2%)
12-17	11 (8.9%)	0	11 (9.2%)	0	11 (6.0%)
≥18	112 (91.1%)	0	82 (68.3%)	0	112 (61.5%)
Racial Group					
White	73 (59.3%)	22 (73.3%)	66 (55.0%)	22 (66.7%)	117 (62.9%)
Asian	Information has been redacted.				
American Indian or Alaska native					
Other					
Not reported due to confidentiality regulations					

Notes: Percentages are based on the number of subjects with non-missing data in each study or overall. Subjects participating in more than one study are counted in both study columns. Each subject is counted only once in the total column. Fourteen subjects from the Phase 1/2a study (SYN-FIXFc-07-001) are excluded from this table as they received a single dose of rFIXFc.

[a] For Study 9HB01EXT, the age used in classifying the subjects into different age categories was the age at entry to the parent study.

Thirty-three (33) subjects (PUPs) with severe hemophilia B (≤2% endogenous FIX activity) received at least one dose of rFIXFc in study 998HB303. For subjects on the episodic treatment regimen, the median number of EDs was 2.5 days (range 0 to 26 days) and the median number of weeks was 22.86 (range 0.3 to164.2 weeks). For subjects on the prophylactic treatment regimen, the median number of EDs was 81.5 days (range 10 to 136 days) and the median number of weeks was 77.5 (range 10.1 to 134.0 weeks). The overall median number of EDs was 76 days (range 1 to137 days) and the overall median number of weeks on treatment was 83.01 (range 6.7 to 226 weeks). Total EDs was 2,233 days. The number of subjects with at least 10 EDs was 28 (84.8%), at least 20 EDs was 26 (78.8%), at least 50 EDs was 21 (63.6%), at least 75 EDs was 18 (54.5%), and at least 100 EDs was 11 (33.3%). The median age was 0.6 years (range 0.08 to 2 years) and the median weight was 9 kg (range 4.6 to 17 kg).

Adverse events were monitored for a total of 57.51 subject-years.

2. Updated version Part II: Module SIV: Post-Authorisation experience

Method used to calculate exposure was not changed.

3. Updated version Part II: Module SVII Identified and potential risks

Safety concerns as reflected in the initial RMP

Summary of safety concerns	
Important identified risks	Inhibitor development to rFIXFc Serious hypersensitivity, serious allergic reaction, and/or anaphylaxis
Important potential risks	Serious vascular thromboembolic events Medication errors

Missing information	Safety profile in patients ≥65 years old Safety profile in women (including pregnant and breast-feeding women) Safety profile in PUPs Use of rFIXFc for ITI

Safety concerns as reflected in the updated RMP version

Summary of Safety Concerns	
Important Identified Risks	Inhibitor development to FIX
Important Potential Risks	Serious vascular thromboembolic events
Missing Information	None

The MAH states that there are no new safety concerns compared to the previous version of the RMP.

In this updated EU RMP (Version 2.1), the previous list of safety concerns has been re-evaluated according to the cumulative post-marketing experience and/or the completed PUP study (Study 998HB303) when applicable and to the European Guideline on Good Pharmacovigilance Practices (GVP)-Module V-Risk management systems (Rev. 2).

The safety concern "Serious hypersensitivity, serious allergic reaction, and/or anaphylaxis" previously classified as important identified risk in the EU RMP (version 2.0) is removed from the list of safety concerns in this updated EU RMP (version 2.1) to be aligned with this updated GVP guidance which recommends including only those important identified risks that warrant further evaluation and risk minimization activities. This risk is communicated in the current product information including relevant instructions as applicable. In addition, in the specialized clinical practice where rFIXFc is used, this risk and its management are known. This risk requires no further characterization or additional risk minimization activities and will only be followed by routine pharmacovigilance.

PRAC Rapp comment:

MAH's arguments are acknowledged and wording as well as intention of GVP module V rev.2 is well known. Hypersensitivity and in particular severe anaphylactic reactions frequently occur in the context of inhibitor development, so that the argument to remove it from identified risks is comprehensible, however, not supported. From the assessor's point of view, it may be advisable to keep hypersensitivity and anaphylactic reactions in identified risks for the moment since besides the association to inhibitor development, the risk also is separately existing and under this aspect a separate class risk for coagulation factor concentrates. Further, RMP section SVII "safety concerns" is directly linked to PSUR section 16.3 "Evaluation of Risks and New information" where MAHs elaborate on the most recent data received for identified and potential risks risks, which is considered especially valuable for periodic re-assessment of the benefit-risk-balance of a product. Taking both into account the MAH is asked to re-include the risk in identified risks of safety concerns moreover since in the currently completed PUP study also a serious hypersensitivity reaction occurred.

In view of Removal of medication errors from potential risks is accepted.

Amendment to missing information is widely accepted, however, missing information on pregnancy and lactation should be kept, since all study participants were males and safety profile in this special female population is not known though being very unlikely to be different from that of males.

Please re-include hypersensitivity and anaphylactic reactions in identified risks and Safety profile in women including pregnant and breast-feeding women in missing information.

4. Updated version Part III: Pharmacovigilance Plan

Updated version Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection for rFIXFc includes:

Specific adverse reaction follow-up questionnaires for the following important risks:

• Inhibitor development to FIX

• ~~Serious hypersensitivity, serious allergic reaction, and/or anaphylaxis~~ *removed*

• Serious vascular thromboembolic events

PRAC Rapp comment:

Please re-include questionnaire for serious hypersensitivity and allergic/anaphylactic reactions due to the above arguments.

Updated Additional Pharmacovigilance activities

Planned and on-going studies

Study/activity type, title, and category	Summary of objectives	Safety concerns addressed	Protocol link Milestones
Data collection from participation in the European Haemophilia Safety Surveillance System (EUHASS) registry. **Category 3**	To monitor the treatment safety of hemophilia B	Inhibitor development to FIX Serious vascular thromboembolic events	**Protocol link: Not applicable** **Milestones:** Data will be reviewed on an on-going basis as part of signal detection and reported within PSURs when available.
Data collection from participation in the European Pediatric Network (PedNet) registry. **Category 3**	To monitor the treatment safety of hemophilia B	Inhibitor development to FIX	**Protocol link: Not applicable** **Milestones:** Data will be reviewed on an on-going basis as part of signal detection and reported within PSURs when available.

Completed studies

Study/activity type, title, and category	Summary of objectives	Safety concerns addressed	Date of Final Study Report submission Link to report
Study 9HB01EXT An Open-Label, Multicenter Evaluation of the Long-Term Safety and Efficacy of Recombinant Human Coagulation Factor IX Fusion Protein (rFIXFc) in the Prevention and Treatment of Bleeding Episodes in Previously Treated Subjects with Hemophilia B (safety extension study, Category 3) **Category 3**	The primary objective of the study is to evaluate the long-term safety of rFIXFc in subjects with hemophilia B. The secondary objective of this study is to evaluate the efficacy of rFIXFc in the prevention and treatment of bleeding episodes in subjects with hemophilia B..	Long-term safety evaluation Safety profile in patients ≥65 years old	27 April 2018 Link to final study report
Study 998HB303 An Open-Label, Multicenter Evaluation of the Safety and Efficacy of Recombinant Coagulation Factor IX Fc Fusion Protein (rFIXFc; BIIB029) in the Prevention and Treatment of Bleeding in Previously Untreated Patients with Severe Hemophilia B (PUPs study), **Category 3**	The primary objective of the study is to evaluate the safety of rFIXFc in PUPs with severe hemophilia B.	Safety profile in PUPs <18 years old Inhibitor development to FIX Use in ITI	18 February 2020 Link to final study report

5. Updated Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Table 2: Ongoing and planned additional pharmacovigilance activities

Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization:				
None				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances:				
None				
Category 3 - Required additional pharmacovigilance activities				
Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Data collection from participation in the European Haemophilia Safety Surveillance System (EUHASS) registry (Ongoing)	To monitor the treatment safety of hemophilia B	Inhibitor development to FIX Serious vascular thromboembolic events	Regular updates	Not applicable. Data will be reviewed on an on-going basis as part of signal detection and will be reported within PSURs when available.
Data collection from participation in the European Pediatric Network (PedNet) registry (Ongoing)	To establish large well-documented birth cohorts of patients with hemophilia, enabling studies on side effects and outcome of treatment	Inhibitor development to FIX	Regular updates	Data will be reviewed on an on-going basis as part of signal detection and will be reported within PSURs when available.

FIX = factor IX; LPLV = last patient last visit; PSUR = Periodic Safety Update Report; PUP = previously untreated patient; rFIXFc = recombinant coagulation factor IX fusion protein.

5. Updated version RMP Part III. V.1. Routine Risk Minimisation Measures

PRAC Rapp comment: *Please amend tables 7 (Description of routine risk minimization measures by safety concern) and 8 (Summary table of pharmacovigilance activities and risk minimization activities by safety concern) accordingly to assessor's request to Part II: Module SVII Identified and potential risks, referring to re-inclusion of hypersensitivity and allergic/anaphylactic reactions in important identified risks.*

6. Updated version RMP Part VI Summary of activities in the risk management plan by product

PRAC Rapp comment: *Please amend summary of the RMP also appropriately*

6.1. Overall conclusion on the RMP

☒ The changes to the RMP are acceptable following 2nd responses submitted on 24 August by MAH

7. Changes to the Product Information

As a result of this variation, section(s) 4.2, 4.8, 5.1 of the SmPC are being updated to incorporate data obtained from the paediatric study of Alprolix in PUPs. The Package Leaflet (PL) is updated accordingly.

The paragraph on PUPs in section 4.2 ("The safety and efficacy of ALPROLIX in previously untreated patients have not yet been established. No data are available.") was removed. This change is in line with the relevant guideline and therefore acceptable.

Changes in section 4.8 comprise an updated tabulated list of adverse reactions and information on factor IX inhibitor development in PUPs.

Inclusion of the adverse reactions "Factor IX inhibition", "Hypersensitivity", and "Injection site erythema" are considered acceptable in principle. However, revisions were considered necessary to adequately reflect these additional adverse reactions in section 4.8.

The tabulated list of adverse reactions proposed at the initial type II variation request showed separate frequencies for PTPs and PUPs, respectively, as can be seen below:

MedDRA System Organ Class	Adverse reactions	Frequency category in PTPs	Frequency category in PUPs
Blood and lymphatic system disorders	Factor IX inhibition		Common*
Immune system disorders	Hypersensitivity		Common*
Metabolism and nutrition disorders	Decreased appetite	Uncommon	
Nervous system disorders	Headache Dizziness Dysgeusia	Common Uncommon Uncommon	

Cardiac disorders	Palpitations	Uncommon	
Vascular disorders	Hypotension	Uncommon	
Gastrointestinal disorders	Paresthesia oral Breath odour	Common Uncommon	
Renal and urinary disorders	Obstructive uropathy Haematuria Renal colic	Common Uncommon Uncommon	
General disorders and administration site conditions	Fatigue Infusion site pain Injection site erythema	Uncommon Uncommon	Common

Except for FIX inhibition and hypersensitivity, this was not considered meaningful. As the differentiation between PTPs and PUPs is only based on their different risk for inhibitor formation, deriving frequencies of adverse reactions from pooled safety data was considered more informative. The MAH had therefore been advised in the first round of assessment to calculate frequencies for injection site erythema and all other adverse reactions (except FIX inhibition and hypersensitivity) based on a pooled analysis of all treated subjects (PTPs + PUPs) as these adverse reactions are not specific to a particular patient group (PTPs or PUPs), and to present them in one single column labelled "Frequency category". This is also in line with the SmPC Guideline that states: "Safety data from several studies should be pooled to increase the precision of adverse reaction rates as appropriate without introducing bias (e.g. major difference in population characteristics or exposure to the product)". The MAH agreed to using a single column ("Frequency category") which is endorsed. However, the MAH did not provide the requested pooled analysis. From the data provided by the MAH, a pooled analysis was not expected to result in changes in frequency categories apart from injection site erythema (which would be changed from "common" to "uncommon"). The MAH was advised that omission of a pooled analysis, can eventually be accepted since the presented frequency category rather overestimates the frequency which can be considered a more conservative approach. Nevertheless, data presentation in section 4.8 needed some further revision, namely the deletion of footnotes indicating differences between PTPs and PUPs apart from FIX inhibition and hypersensitivity. This was revised accordingly after the second round of assessment.

In contrast, for FIX inhibition and hypersensitivity occurring during the PUP study, the frequency derived from PUPs only is considered adequate. The MAH was asked to clearly state in a footnote that both events of Factor IX inhibition and hypersensitivity occurred in a single previously untreated patient, and that calculation of frequency is not based on all treated subjects but in this case only on PUPs. This issue has been resolved.

It is acknowledged that the precision of the inhibitor incidence in study 998HB303 is low (3.03% [95% CI: 0.08%, 15.76%]). It is therefore not considered adequate to use this for comparison against any other products. However, as the frequency deriving from the study results is also in line with that generally stated in the FIX guideline ("Inhibitors to factor IX have been demonstrated in approximately 4% of patients with severe haemophilia B") it is considered justified to state the frequency of "common" in the SmPC despite the possibility of a true inhibitor incidence of 15.76% (upper limit of the 95% CI). Anyway, according to the SmPC GL frequency should represent crude incidence rates and therefore the frequency category "common" is applicable.

Changes in section 5.1. pertain to efficacy and safety information derived from the PUP study. Results were proposed to be added in accordance with results from studies in PTPs. The MAH was asked to make it more clear to the reader that ABR is not comparable between different factor concentrates and between different clinical studies. The corresponding sentence derived from the Factor IX core SmPC guideline was shifted within section "Clinical efficacy and safety" as indicated.

Initially, it was unclear, why a considerable high number of PUPs had not completed the visits for inhibitor

testing which might have impacted on reported inhibitor frequencies. Additionally, uncertainties in this patient group regarding annualized Alprolix consumption, high numbers of injections to treat a single bleed in 2 subjects and follow up-data on the subject who developed a factor IX inhibitor (and hypersensitivity) existed. These concerns were expressed during the assessment of the P46 procedure (ongoing at that time) and were subject of request for additional clarification. To date, these concerns on efficacy and safety have been adequately addressed by the MAH in the response to the P46 assessment report. Therefore, no outstanding issues on safety or efficacy remain.

Comments were provided in commented Product Information.

8. Request for supplementary information

8.1. Major objections

None.

8.2. Other concerns

1. In section 4.8 the following changes are necessary:

   The MAH should calculate frequencies for injection site erythema and all other adverse reactions (except FIX inhibition and hypersensitivity) based on a pooled analysis of all treated subjects (PTPs + PUPs) and present them in one single column labelled "Frequency category". For FIX inhibition and hypersensitivity occurring during the PUP study, the frequency derived from PUPs only is considered adequate. It should be clearly stated in a footnote that both events of Factor IX inhibition and hypersensitivity occurred in a single previously untreated patient, and that calculation of frequency is not based on all treated subjects but in this case only on PUPs. Other minor revisions in this section are requested (comments provided in Product Information).

2. The basis for the proposed changes of the Product Information is study 998HB303 which was submitted and assessed during EMEA/H/C/004142/P46 006. Additional clarification as requested during the P46 procedure is also necessary for assessment of the PI changes. The MAH is therefore asked to address the following questions (identical to the questions raised in the above mentioned P46 procedure):

   - The MAH is asked to provide any follow-up data on patient who discontinued the study due to inhibitor development, if available.
   - The MAH is asked for clarification why a considerable high number of subjects did not complete the visits for inhibitor testing. Furthermore, a discussion is awaited whether detection of any inhibitors potentially occurring during the study was possible in light of the poor adherence to study visits.
   - The MAH is asked to discuss the following two bleeding episodes in two subjects in more detail and to explain the high number of injections needed for resolution:
   - The median annualized rFIXFc consumption was 203.2 IU/kg (range 0 to 5719 IU/kg) in the episodic treatment arm and 3175.0 IU/kg (range 2544 to 13164 IU/kg) in the prophylaxis treatment arm. The overall median annualized rFIXFc consumption was reported as 2673.3 IU/kg (range 0 to 10507 IU/kg). Clarification is needed regarding discrepancies in ranges (shown as min and max values) of the overall median annualized consumption.

- No patient response was provided for a high number of injections: 58 (72.5%) in the episodic treatment arm and 17 (23.0%) in the prophylactic treatment arm, respectively. The MAH is asked to clarify why no reports were received for such a high number of bleeding episodes and to discuss the interpretability of results.

8.2.1. RMP

3. *Please re-include hypersensitivity and anaphylactic reactions in identified risks and Safety profile in women including pregnant and breast-feeding women in missing information.*
4. *Please re-include questionnaire for serious hypersensitivity and allergic/anaphylactic reactions.*
5. *Please amend tables 7 and 8 accordingly to request in Part II: Module SVII Identified and potential risks, referring to re-inclusion of hypersensitivity and allergic/anaphylactic reactions in important identified risks.*
6. *Please amend summary of the RMP also appropriately.*

9. Assessment of the responses to the request for supplementary information

9.1. Major objections

None

9.2. Other concerns

Question 1:

In section 4.8 the following changes are necessary:

The MAH should calculate frequencies for injection site erythema and all other adverse reactions (except FIX inhibition and hypersensitivity) based on a pooled analysis of all treated subjects (PTPs + PUPs) and present them in one single column labelled "Frequency category". For FIX inhibition and hypersensitivity occurring during the PUP study, the frequency derived from PUPs only is considered adequate. It should be clearly stated in a footnote that both events of Factor IX inhibition and hypersensitivity occurred in a single previously untreated patient, and that calculation of frequency is not based on all treated subjects but in this case only on PUPs. Other minor revisions in this section are requested (see comments in Product Information).

Summary of MAH's responses:

Data from a total of 153 PTPs and 33 PUPs is available from the clinical development program. In total, there were 3 ADRs identified in PUPs, none of which overlapped with ADRs observed in PTPs. Taking the different treatment backgrounds of PTP and PUP populations into account, the MAH considers that there would be a very limited additional benefit of performing a pooled analysis of all treated subjects.

We acknowledge the benefits of presenting frequencies in a single column and propose a change where footnotes are used to clarify the data sources. We also propose additional information on the factor IX inhibition and hypersensitivity under the subheading Description of selected adverse reactions.

Assessment of MAH's responses:

The MAH states that data from 153 PTPs and 33 PUPs are available from the clinical development program. A total of 3 ADRs were identified in PUPs, none of which overlapped with ADRs in PTPs. The MAH argues that pooled ADR analysis would only add very limited additional benefit considering the different treatment backgrounds of the two populations and did not provide the requested pooled analysis. However, differentiation between PUPs and PTPs in Section 4.8 could be misleading, and a tabulated list of adverse events reflecting the entire haemophilia B population studied without further sub-division is considered more appropriate. The only exceptions are the two ADRs factor IX inhibition and hypersensitivity, with respective frequencies being specific for PUPs (as both events are known to occur with higher frequency in PUPs than in PTPs in haemophilia B). All other ADRs shall be presented for the entire haemophilia B population. From the data provided by the MAH, a pooled analysis is not expected to result in changes in frequency categories apart from injection site erythema (which would be changed from "common" to "uncommon"). Yet, if the MAH prefers to omit a pooled analysis, this can eventually be accepted since the presented frequency category rather overestimates the frequency which can be considered a more conservative approach. Nevertheless, data presentation in section 4.8 needs some further revision, namely the deletion of footnotes indicating differences between PTPs and PUPs apart from FIX inhibition and hypersensitivity.

The MAH submitted an updated SmPC adequately incorporating the abovementioned requests.

Conclusion:

Issue resolved.

Question 2:

The basis for the proposed changes of the Product Information is study 998HB303 which was submitted and assessed during EMEA/H/C/004142/P46 006. Additional clarification as requested during the P46 procedure is also necessary for assessment of the PI changes. The MAH is therefore asked to address the following questions (identical to the questions raised in the above mentioned P46 procedure):

- The MAH is asked to provide any follow-up data on patient who discontinued the study due to inhibitor development, if available.
- The MAH is asked for clarification why a considerable high number of subjects did not complete the visits for inhibitor testing. Furthermore, a discussion is awaited whether detection of any inhibitors potentially occurring during the study was possible in light of the poor adherence to study visits.
- The MAH is asked to discuss the following two bleeding episodes in two subjects in more detail and to explain the high number of injections needed for resolution:
- The median annualised rFIXFc consumption was 203.2 IU/kg (range 0 to 5719 IU/kg) in the episodic treatment arm and 3175.0 IU/kg (range 2544 to 13164 IU/kg) in the prophylaxis treatment arm. The overall median annualized rFIXFc consumption was reported as 2673.3 IU/kg (range 0 to 10507 IU/kg). Clarification is needed regarding discrepancies in ranges (shown as min and max values) of the overall median annualized consumption.
- No patient response was provided for a high number of injections: 58 (72.5%) in the episodic treatment arm and 17 (23.0%) in the prophylactic treatment arm, respectively. The MAH is asked to clarify why no reports were received for such a high number of bleeding episodes and to discuss the interpretability of results.

Summary of MAH's responses:

The response to these questions has been submitted on 4 June 2020 as part of the ongoing procedure EMEA/H/C/004142/P46/006.

Assessment of MAH's responses:

The MAH has provided responses to all points of question 2 as part of the procedure EMEA/H/C/004142/P46/006, adequately addressing these issues.

Conclusion:

Issue resolved.

RMP:

Question 3:

Please re-include hypersensitivity and anaphylactic reactions in identified risks and Safety profile in women including pregnant and breast-feeding women in missing information.

Summary of MAH's responses:

The MAH agree to reintroduce "Serious hypersensitivity" as an important identified risk, the MAH suggest revising title of the safety concern to "Serious hypersensitivity" as this would also include serious allergic reactions including anaphylaxis.

The RMP Part II: Module SVII Identified and potential risks and other relevant sections, has been updated accordingly.

The MAH disagree to re-include "Use in women including pregnant and breast-feeding women" as the revised GVP guidance states that the absence of data itself (e.g. exclusion of a population from clinical studies) does not automatically constitute a safety concern. Also:

- The target population for Alprolix is predominantly male, and although female patients were not included in the clinical studies the MAH agrees with Assessors comment that the safety profile in this special female population is not known though being very unlikely to be different from that of males.
- Information regarding use in pregnancy and breast-feeding is described in SmPC
- There are no additional Pharmacovigilance activities to further characterize use in female patients
- Routine pharmacovigilance activities would ensure all reports of special situations, *i.e.* use during pregnancy and lactation, are followed-up thoroughly.
- Information on use in pregnant or lactating women will be presented in PSURs, as post-authorization use in special populations, as applicable.

Assessment of MAH's responses:

The MAH's arguments are acknowledged regarding the main target population as well as the presumably rather similar safety profile in women. In view of pregnancy and lactation there might be significant differences, however, in terms of the rarity of such treatment current routine pharmacovigilance (including special follow-up for pregnancy cases) measures may be sufficient.

Conclusion:

Issues resolved.

Question 4:

Please re-include questionnaire for serious hypersensitivity and allergic/anaphylactic reactions.

Summary of MAH's responses:

The questionnaire for serious hypersensitivity and allergic/anaphylactic reactions has been re-included in the RMP (Annex 4).

Assessment of MAH's responses:

The MAH has re-introduced the questionnaires as requested.

Conclusion:

Issues resolved.

Question 5:

Please amend tables accordingly to request in Part II: Module SVII Identified and potential risks, referring to re-inclusion of hypersensitivity and allergic/anaphylactic reactions in important identified risks.

Summary of MAH's responses:

The RMP Table 5 was incorrect and was amended accordingly.

Assessment of MAH's responses:

There was a mistake in one of the tables in the RMP (i.e. Serious hypersensitivity was re-introduced in wrong row; under important potential risks, it should remain as an important identified risk).

Updated conclusion following second round of responses:

Updated correct tables were provided.

Conclusion:

Issue resolved.

Question 6:

Please amend summary of the RMP also appropriately.

Summary of MAH's responses:

The RMP summary has been amended accordingly.

Assessment of MAH's responses:

The RMP Summary was amended accordingly.

Updated conclusion following submission of an updated RMP:

Updated correct tables were provided.

Conclusion:

Issue resolved.

10. Appendix 1: P46 AR