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SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee (PRAC)

Assessment report

Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Active substances: human coagulation factor VIII; efmoroctocog alfa; moroctocog alfa; octocog alfa; simoctocog alfa; susoctocog alfa; turoctocog alfa

Procedure number(s): EMEA/H/A-31/1448

Advate EMEA/H/C/0520/A31/0078
Elocta EMEA/H/C/3964/A31/0006
Helixate Nexgen EMEA/H/C/0276/A31/0178
Iblias EMEA/H/C/4147/A31/0002
Kogenate Bayer EMEA/H/C/0275/A31/0185
Kovaltry EMEA/H/C/3825/A31/0004
NovoEight EMEA/H/C/2719/A31/0014
Nuwiq EMEA/H/C/2813/A31/0015
Obizur EMEA/H/C/2792/A31/0003
Refacto AF EMEA/H/C/0232/A31/0134
Voncento EMEA/H/C/2493/A31/0022

Note:

Assessment report as adopted by the PRAC and considered by the CHMP with all information of a commercially confidential nature deleted.



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1. Information on the procedure

In May 2016, an open-label, randomised controlled trial aimed at addressing the incidence of inhibitors between the two classes (pdFVIII vs. rFVIII products) was published in the New England Journal of Medicine¹. This trial, known as the SIPPET study (“Survey of Inhibitors in Plasma-Product Exposed Toddlers”) was conducted to evaluate the relative risk of inhibitors in patients treated with pdFVIII compared to rFVIII. It found that patients treated with rFVIII products had an 87 % higher incidence of all inhibitors than those treated with pdFVIII (which contained VWF) (hazard ratio, 1.87; 95% CI, 1.17 to 2.96).

On 6 July 2016 Paul-Ehrlich-Institut Germany initiated a referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, and requested the PRAC to assess the impact of the results of the SIPPET study on the benefit-risk balance of human and recombinant coagulation factor VIII containing medicinal products and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked.

2. Scientific discussion

2.1. Introduction

Treatment of congenital haemophilia is currently based on prophylactic or on-demand replacement therapy with coagulation factor VIII (FVIII). FVIII replacement therapy can be generally categorised into two broad classes of products; plasma derived (pdFVIII) and recombinant (rFVIII) FVIII. A wide range of individual pdFVIII and rFVIII products are authorised for use in the European Union.

A major complication of FVIII therapy is the occurrence of IgG alloantibodies (inhibitors) that neutralise FVIII activity, causing loss of bleeding control. Treatment of patients who have developed inhibitors requires careful individual management and can be resistant to therapy.

Treatment with both pdFVIII and rFVIII can lead to development of inhibitors (tested with the Nijmegen method of the Bethesda assay and defined as ≥ 0.6 Bethesda units (BU) for “a low titre” inhibitor and >5 BU for a “high-titre” inhibitor).

The occurrence of inhibitor development in haemophilia A patients receiving FVIII products mostly occurs in previously-untreated patients (PUPs) or minimally treated patients (MTPs) who are still within the first 50 days of exposure (EDs) to the treatment. Inhibitors are less likely to occur in previously-treated patients (PTPs).

The known risk factors for inhibitor development can be grouped into patient and treatment-related factors:

- Patient-related risk factors include type of F8 gene mutation (e.g. null and large mutations carry highest risk), severity of haemophilia (those with severe haemophilia A are at highest risk), ethnicity (studies have suggested that Caucasians have a lower risk than other ethnicities), family history of inhibitor development and possibly HLA-DR (Human Leukocyte Antigen - antigen D Related) constitution.

¹ F. Peyvandi et al. “A Randomized Trial of Factor VIII and Neutralizing Antibodies in Hemophilia A” N Engl J Med. 2016 May 26; 374(21):2054-64

- Treatment-related factors include intensity of exposure, number of exposure days (EDs), on demand treatment posing a greater risk than prophylaxis, particularly in the context of danger signals such as trauma, surgery, and young age at first treatment poses a higher risk.

Whether there are significant differences in the risk of inhibitor development between different types of FVIII replacement product remains an area of uncertainty. Differences between products in each FVIII class and consequently differential risks between individual products, are biologically plausible. The pdFVIII class consists of products with or without Von Willebrand Factor (VWF), and those with VWF contain a range of VWF levels. Some experimental studies have suggested a role for VWF in protecting FVIII epitopes from recognition by the antigen-presenting cells, thereby reducing immunogenicity, although this remains theoretical. VWF is not present in rFVIII, but there is significant heterogeneity within the rFVIII class for instance due to the different manufacturing processes used, with a wide range of products from different manufacturers produced over the past 20 years. These different manufacturing processes (including the different cell lines used to engineer the rFVIII products) can in theory lead to differential immunogenicity.

Further to the recent publication on the SIPPET study, the MAHs were requested to assess the potential impact of the results of this study and other relevant safety data on inhibitor development in PUPs on the MA of their FVIII product including consideration on risk minimisation measures.

The lead authors of the SIPPET study were also invited to respond to a list of questions regarding the study methods and findings and to present their conclusions at the February 2017 PRAC plenary meeting. Information submitted by the lead authors of the SIPPET study during the course of the referral was also taken into consideration by PRAC in reaching its conclusion.

2.2. Clinical discussion

Published observational studies

The responses of MAHs referred to a range of published observational studies (the CANAL, RODIN, FranceCoag, UKHCDO, amongst others) which have sought to evaluate any differential risks of inhibitor development between the classes of pdFVIII and rFVIII, as well as any differential risk of inhibitor development between products within the rFVIII class.

These studies have yielded different results and suffer from the limitations of observational studies, and in particular from possible selection bias. The risk of inhibitor development is multifactorial (aside from any putative product-specific risk), and such studies have not always been able to collect information on relevant covariates and to adjust the analyses accordingly; residual confounding is inevitably a significant uncertainty. Furthermore, over time there have been changes in manufacturing process of individual products and changes in treatment regimens between centres, hence “like for like” comparisons between products is not always possible. These factors make control of such studies and interpretation of the results challenging.

The CANAL study² found no evidence of a class difference, including pdFVIII products with considerable quantities of von Willebrand factor; for ‘clinically relevant’ inhibitors the adjusted hazard ratio was 0.7 (95% CI 0.4-1.1), and for high titre inhibitors (≥ 5 BU) was 0.8 (95% CI 0.4-1.3).

² <http://www.bloodjournal.org/content/109/11/4648.full.pdf>

The RODIN/Pednet study³ also found no evidence of a class difference in inhibitor risk between all pdFVIII vs all rFVIII; for 'clinically relevant' inhibitors the adjusted hazard ratio was 0.96 (95% CI 0.62-1.49), and for high titre inhibitors (≥ 5 BU/ml) was 0.95 (95% CI 0.56-1.61). However, the study found evidence of an increased risk of inhibitors (all and high titre) for 2nd generation rFVIII octocog alfa (Kogenate FS/Helixate NexGen) compared with 3rd generation rFVIII octocog alfa (which was driven solely by data for Advate).

This signal of significant increased risk of inhibitors (all and high titre) for 2nd compared with 3rd generation rFVIII then became the focus of two European reviews. First, in relation to the RODIN/Pednet findings, the Pharmacovigilance Risk Assessment Committee (PRAC) / Committee for Medicinal Products for Human Use (CHMP) - EMA/781158/2013⁴) concluded in 2013 within a referral under Article 20 of Regulation (EC) No 726/2004 that the data were not sufficiently robust to support a conclusion that Kogenate FS/Helixate NexGen was associated with an increased risk of developing factor VIII inhibitors compared with other products. The PRAC/ CHMP considered that when all the available data were taken into account, they were consistent with the general clinical experience that most inhibitors develop within the first 20 days of exposure.

Two studies were then published in 2014, the UKHCDO and FranceCoag studies, that further evaluated the 'signal' generated by the RODIN/Pednet study. These studies evaluated only rFVIII products, and did not include pdFVIII products.

Similar to RODIN/Pednet, the UKHCDO study found a significant increased risk of inhibitors (all and high titre) for Kogenate FS/Helixate NexGen (2nd generation rFVIII) compared to Advate (3rd generation rFVIII). Although this became non-significant when UK patients (also included in the RODIN/Pednet study) were excluded. There was also evidence for an increased risk with Refacto AF (another 3rd generation rFVIII) vs Advate, but only for all inhibitor development. Like the UKHCDO study, the FranceCoag study also found no statistically significant increased risk for any rFVIII products vs Advate when French patients (also in the RODIN/Pednet study) were excluded.

The findings of UKHCDO and FranceCoag studies prompted a raw data meta-analysis of all three studies (RODIN/Pednet, UKHCDO and FranceCoag studies). The PRAC assessed this meta-analysis in a signal procedure in 2016. A total of 1,102 PUPs (481 RODIN, 293 FranceCoag and 328 UKHCDO) for whom data on exposure to recombinant factor VIII are available were included in this meta-analysis. The meta-analysis suggested a trend towards an increase of high-titre inhibitor development and all inhibitor development with Kogenate Bayer compared to Advate. Overall, 147 out of 400 PUPs treated with Kogenate Bayer / Helixate Nexgen (37%) developed inhibitory antibodies, of which 88 (22%) had high-titre inhibitors. For Advate, a total of 100 out of 385 PUPs (26%) treated with the medicine developed inhibitors, of which 57 (15%) had high-titre inhibitors. The percentages are similar for the study period from 2004 onwards when both products were licensed in parallel. A similar trend was also observed for other recombinant factor VIII products. However, the results are even less pronounced due to sample size constraints.

Although the meta-analysis was well conducted, the PRAC noted several limitations including the possibility of residual confounding in the three studies, which cannot be corrected for in the meta-analysis. Furthermore, PRAC acknowledged that inhibitor development is multifactorial, where a number of parameters may have an impact on the incidence in PUPs, and that adjusting for all of these factors in the analyses may not be possible. PRAC also noted that there has been no signal for a similar

³ Gouw SC et al. PedNet and RODIN Study Group. Factor VIII products and inhibitor development in severe hemophilia A. *N Engl J Med* 2013; 368: 231-9. - <http://www.bloodjournal.org/content/121/20/4046.full.pdf>

⁴ EMA/781158/2013 http://www.ema.europa.eu/docs/en_GB/document_library/Press_release/2013/12/WC500158681.pdf

trend of increases in inhibitor incidences with Kogenate Bayer in PTPs in other studies, a population where the experience with this product is large.

It was noted that the PRAC had agreed in 2016 that the currently available evidence does not confirm that Kogenate Bayer/Helixate NexGen is associated with an increased risk of factor VIII inhibitors, compared with other recombinant factor VIII products in previously untreated patients (EMA/PRAC/332348/2016⁵). These conclusions were consistent with the previous conclusions drawn by the PRAC in 2013.

MAH-sponsored studies

The MAHs provided an analysis of low and high titre inhibitor development in PUPs with severe haemophilia A (FVIII < 1%) from all clinical trials and observational studies conducted with their products, along with critical discussion on the limitations of these studies.

The data came from a very wide range of heterogeneous studies across products and over time. Many of these studies were small and not specifically designed to evaluate the inhibitor risk in PUPs with severe haemophilia A. The studies were mostly single arm and do not provide data to perform comparative analysis (either between pdFVIII and rFVIII as a class comparison, or within the rFVIII class). However, the general estimates of inhibitor rates from these studies for individual products are broadly in line with the findings from large observational studies.

Of the larger and more relevant studies for pdFVIII products, inhibitor rates observed (often not stated if high or low titre) ranged from 3.5 to 33%, with most around 10-25%. However, in many cases little information was provided on the methods, patient populations and nature of the inhibitors to assess the information in the context of more recent published data. For most rFVIII products, newer and more relevant information from clinical trials in PUPs is available. Inhibitor rates in these studies range from 15 to 38% for all inhibitors and 9 to 22.6% for high titre inhibitors; i.e. within the range of 'very common'.

The PRAC also considered interim results submitted by the MAHs from ongoing studies from CSL (CRD019_5001) and Bayer (Leopold KIDS, 13400, part B.).

Furthermore, the PRAC examined clinical trials and the scientific literature for *de novo* inhibitors in PTPs. The analysis demonstrated that the frequency of inhibitor development is much lower in PTPs compared to PUPs. The available data showed that in many studies including the EUHASS registry (Iorio A, 2017⁶; Fischer K, 2015⁷) the frequency could be classified as "uncommon".

The SIPPET study

The SIPPET study was an open-label, randomized, multi-centre, multi-national trial investigating the incidence of neutralising allo-antibodies in patients with severe congenital haemophilia A (plasma FVIII

⁵ EMA/PRAC/332348/2016 http://www.ema.europa.eu/docs/en_GB/document_library/Report/2016/05/WC500206411.pdf

⁶ Iorio A, Barbara AM, Makris M, Fischer K, Castaman G, Catarino C, Gilman E, Kavakli K, Lambert T, Lassila R, Lissitchkov I, Mauser-Bunschoten E, Mingot-Castellano ME, Ozdemir N1, Pabinger I, Parra R1, Pasi J, Peerlinck K, Rauch A6, Rousset-Robert V, Serban M, Tagliaferri A, Windyga J, Zanon E: Natural history and clinical characteristics of inhibitors in previously treated haemophilia A patients: a case series. *Haemophilia*. 2017 Mar; 23(2): 255-263. doi: 10.1111/hae.13167. Epub 2017 Feb 15.

⁷ Fischer K, Lassila R, Peyvandi F, Calizzani G, Gatt A, Lambert T, Windyga J, Iorio A, Gilman E, Makris M: EUHASS participants Inhibitor development in haemophilia according to concentrate. Four-year results from the European HAemophilia Safety Surveillance (EUHASS) project. *Thromb Haemost*. 2015 May; 113(5): 968-75. doi: 10.1160/TH14-10-0826. Epub 2015 Jan 8.

concentration < 1%) with either the use of pdFVIII or rFVIII concentrates. Eligible patients (< 6 years, male, severe haemophilia A, no previous treatment with any FVIII concentrate or only minimal treatment with blood components) were included from 42 sites. The primary and secondary outcomes assessed in the study were the incidence of all inhibitors (≥ 0.4 BU/mL) and the incidence of high-titre inhibitors (≥ 5 BU/mL), respectively.

Inhibitors developed in 76 patients, 50 of whom had high-titre inhibitors (≥ 5 BU). Inhibitors developed in 29 of the 125 patients treated with pdFVIII (20 patients had high-titre inhibitors) and in 47 of the 126 patients treated with rFVIII (30 patients had high-titre inhibitors). The cumulative incidence of all inhibitors was 26.8% (95% confidence interval [CI], 18.4 to 35.2) with pdFVIII and 44.5% (95% CI, 34.7 to 54.3) with rFVIII; the cumulative incidence of high-titre inhibitors was 18.6% (95% CI, 11.2 to 26.0) and 28.4% (95% CI, 19.6 to 37.2), respectively. In Cox regression models for the primary end point of all inhibitors, rFVIII was associated with an 87% higher incidence than pdFVIII (hazard ratio, 1.87; 95% CI, 1.17 to 2.96). This association was consistently observed in multivariable analysis. For high-titre inhibitors, the hazard ratio was 1.69 (95% CI, 0.96 to 2.98).

The PRAC considered that as a prospective randomised trial, the SIPPET study avoided many of the design limitations of the observational and registry-based studies undertaken so far to evaluate the risk of inhibitor development in PUPs. However the PRAC is of the view that there are uncertainties with regards to the findings of the SIPPET study which preclude the conclusion that there is a higher risk of inhibitor development in PUPs treated with rFVIII products than pdFVIII products studied in this clinical trial, as detailed below:

- The SIPPET analysis does not allow for product-specific conclusions to be made as it relates only to a small number of certain FVIII products. The study was not designed and powered to generate sufficient product-specific data and, therefore, to draw any conclusions on the risk of inhibitor development for individual products. In particular, only 13 patients (10% of the FVIII arm) received a third generation rFVIII product. However, despite the lack of robust evidence to support differential risks between rFVIII products, differential risks cannot be excluded, as this is a heterogeneous product class with differences in composition and formulations. Therefore, there is a high degree of uncertainty around extrapolating the SIPPET findings to the entire rFVIII class, particularly for more recently-authorized rFVIII products which were not included in the SIPPET trial.
- The SIPPET study has methodological limitations, with particular uncertainty around whether the randomisation process (block size of 2) may have introduced a selection bias in the study.
- There were also deviations from the final protocol and statistical analysis plan. The statistical concerns include the fact that no pre-specified primary analysis has been published and the fact that the study was stopped early following the publication of the RODIN study indicating that Kogenate FS might be associated with an increased risk of inhibitor formation. Although this could not have been prevented, an early termination of an open label trial raises the possibility of investigator bias and inflation of the probability of detecting an effect that is not present.
- Treatment regimens in EU are different from those in the SIPPET study. The relevance for clinical practice in the EU (and therefore for the products subject to this procedure) is therefore questioned. It is uncertain whether the findings of SIPPET can be extrapolated to the risk of inhibitors in PUPs in current clinical practice in the EU as treatment modality and intensity have been suggested as risk factors for inhibitor development in previous studies. Importantly, the EU SmPCs do not include modified prophylaxis (as defined in the SIPPET study) as an

authorised posology, and the impact of the apparent imbalance in the unspecified other combinations of treatment modality on the SIPPET findings is unclear. Therefore, it remains uncertain whether the same differential risk of inhibitor development observed in the SIPPET study would be apparent in patient populations treated in routine care in other countries where the modality of treatment (i.e. primary prophylaxis) is different from that in the study. The additional points of clarification provided by the SIPPET authors do not fully resolve this uncertainty.

Having considered the abovementioned results from SIPPET, the published literature and all the information submitted by the MAHs, as well as the views expressed by experts expressed at the *ad-hoc* expert meeting, the PRAC concluded that:

- Inhibitor development is an identified risk with both pdFVIII and rFVIII products. Although the clinical studies for some individual products have identified limited numbers of cases of inhibitor development, these tend to be small studies with methodological limitations, or studies not adequately designed to evaluate this risk.
- The FVIII products are heterogenous, and the plausibility of different rates of inhibitor development between individual products cannot be excluded.
- Individual studies have identified a wide range of inhibitor development across products, but the direct comparability of study results is questionable based on diversity of study methods and patient populations over time.
- The SIPPET study was not designed to evaluate the risk of inhibitor development for individual products, and included a limited number of FVIII products. Due to heterogeneity across products, there is considerable uncertainty in extrapolating the findings of studies that have evaluated only class effects to individual products; and particularly to products (including more recently authorised products) which are not included in such studies.
- Finally, the PRAC noted that to date most studies evaluating a differential risk of inhibitor development between classes of FVIII products suffer from a variety of potential methodological limitations and based on the available data considered there is no clear and consistent evidence to suggest differences in relative risk between classes of FVIII products. Specifically, the findings from the SIPPET study, as well as those from the individual clinical trials and observational studies included in the MAH responses, are not sufficient to confirm any consistent statistically and clinically meaningful differences in inhibitor risk between the rFVIII and pdFVIII product classes.

Further to the assessment of the totality of the responses submitted by the MAH for susoctocog alfa (Obizur), the PRAC is of the opinion that the outcome of this article 31 referral procedure does not apply to this product in view of the indication of Obizur (acquired haemophilia A due to inhibitory antibodies to endogenous FVIII) and the different target population.

3. Expert consultation

The PRAC consulted an ad hoc expert group on 22 February 2017.

The PRAC considered the views expressed by experts during an ad-hoc meeting. The expert group was of the view that the relevant available data sources have been considered. The expert group suggested

that further data are needed to establish if there are clinically relevant differences in frequency of inhibitor development between different factor VIII products and that, in principle, such data should be collected separately for individual products, as degree of immunogenicity will be difficult to generalise across the classes of products (i.e. recombinant vs. plasma-derived).

The experts also agreed that the degree of immunogenicity of different products was adequately described overall with the amendments to the SmPC proposed by the PRAC highlighting the clinical relevance of inhibitor development (in particular low compared to high titre inhibitors), as well as the frequency of 'very common' in PUPs and 'uncommon' in PTPs. The experts also suggested studies which could further characterise the immunogenic properties of the factor VIII medicinal products (e.g. mechanistic, observational studies).

4. Benefit-risk balance

4.1. Initial benefit-risk balance assessment

Based on the current evidence from the SIPPET study, as well as data from the individual clinical trials and observational studies included in the MAH responses, and the views expressed by the experts of the *ad-hoc* expert meeting, the PRAC agreed that the current evidence does not provide clear and consistent evidence of any statistically and clinically meaningful differences in inhibitor risk between rFVIII and pdFVIII products. No conclusions can be drawn on any role of VWF in protecting against inhibitor development.

Given these are heterogenous products, this does not preclude individual products being associated with an increased risk of inhibitor development in ongoing or future PUP studies.

Individual studies have identified a wide range of inhibitor frequency in PUPs across products, and the SIPPET study was not designed to differentiate between individual products in each class. Due to very different study methods and patient populations that have been studied over time, and inconsistent findings across studies, the PRAC found that the totality of evidence does not support a conclusion that recombinant factor VIII medicines, as a class, poses a greater risk of inhibitor development than the class derived from plasma.

Besides, the PRAC noted that several FVIII products currently include in their product information reference to data from study results which do not allow a definite conclusion on the inhibitor risk for individual products. As the evidence suggests that all human FVIII products carry a risk of inhibitor development, within the frequency of 'very common' and 'uncommon' for PUPs and PTPs respectively, the PRAC recommends that the SmPCs should be aligned with these frequencies unless justified by product specific data.

In view of the above, the PRAC concluded that the benefit-risk balance of Factor VIII products indicated as for the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency), remains favourable subject to the changes to the product information agreed (section 4.4, 4.8 and 5.1 of the SmPC).

4.2. Re-examination procedure

Following the adoption of the PRAC recommendation in May 2017, a re-examination request was received from one of the MAHs involved in the procedure, LFB Biomedicaments, on 26 May 2017. The detailed grounds for re-examination from LFB Biomedicaments, were received on 5 July 2017.

4.2.1. Detailed grounds for re-examination submitted by LFB Biomedicaments

The grounds for re-examination of the PRAC recommendation as submitted by LFB Biomedicaments are summarised below:

Evidence from the SIPPET study

LFB Biomedicaments claimed that SIPPET study, which is the first randomised controlled trial (RCT) designed as a superiority study, and published in the peer-reviewed New England Journal of Medicine (NEJM), demonstrates results that are consistent with that of other publications presenting multivariable analyses or adjustment for cofounders. In addition, LFB Biomedicaments considered that SIPPET publication brings an important piece of new scientific knowledge that needs to be taken into account, although some reservations might be made on extrapolation to single FVIII products.

LFB Biomedicaments states that SIPPET study has shown a higher risk in inhibitor development of the recombinant FVIII products as compared to plasma-derived ones and LFB Biomedicaments believes that not reflecting this information in the product information of human and recombinant coagulation factor VIII containing medicinal products would lead the prescribers to be prompted to prescribe recombinant products, having their patients losing a chance to minimise inhibitor development.

Required level of evidence from inhibitor development studies

LFB Biomedicaments agrees with the May 2017 PRAC Recommendation of requesting specific prospective studies for new factor VIII products, although the feasibility of such PUPs studies is to be assessed. The MAH's view is that not only clinical trials would bring relevant information on the risk of inhibitor development but also post-marketing studies, whether prospective retrospective, interventional or non-interventional.

LFB Biomedicaments claimed that most of pdFVIII products were developed before the implementation of the paediatric regulation and most of rFVIII products after, and thus, the choice of this milestone is thought to introduce a severe bias for the selection of data allowed to be mentioned in the SmPCs. PUPs population is rare and thus, the statistical power in case of specific interventional clinical study is difficult to reach. It is also LFB Biomedicament's view that the PIP process does not bring any further assurance of the robustness of the data in the specific context of inhibitor occurrence analysis (as they have low statistical power), but instead brings a bias in favour of the Factor VIII recombinant medicinal products.

Risk communication of product-specific data on inhibitor development

LFB Biomedicaments does not agree with the removal of reference to data from study results currently included in sections 4.8 and 5.1 of the SmPCs, and consequently the removal of the results on the incidence of inhibitors from the LFB Retrospective study from the SmPC of Factane, as they consider these data useful for the prescribers in order to inform the patients about the inhibitor development risk.

Furthermore, LFB Biomedicaments argues that the absence of such information in the SmPCs for plasma-derived products will not give the chance to prescribers to compare inhibitor development incidence of individual products or across the two classes of products (recombinant and plasma derived). This would attract prescribers towards products with PUPs studies mentioned in their SmPC over products without mention of PUP study.

4.2.2. PRAC discussion on grounds for re-examination

The PRAC carefully considered the detailed grounds for re-examination by LFB Biomedicaments together with the underlying data for these grounds.

Evidence from the SIPPET study

While it is acknowledged that SIPPET study is a large randomized trial of interest, important uncertainties on the methodology and the results remain. Indeed several weaknesses and bias are noted such as the potentially biased patient selection due to randomisation with block size, the choice of products and centres and the central laboratory testing of all samples.

Also, important concerns were raised on the extrapolation of the results to the wide range of existing plasma-derived and recombinant FVIII medicines. Only a total of 8 products (4 plasma-derived and 4 recombinant factor VIII medicinal products) were included in the SIPPET study.

Besides, the important variability of the two classes of FVIII products (composition, FVIII activity, VWF content and conformation, glycosylation, HCP or impurities ...) make it impossible to draw a general conclusion on a class level.

PRAC also considered that a differential class-specific risk for the full range of the authorised medicinal products would need to be based on robust evidence that would allow assuming homogeneity within each of the two classes of pdFVIII- and the rFVIII-products, respectively.

Considering all these uncertainties, the PRAC maintains its view that the results of the SIPPET study are not suitable to draw conclusion on difference in the risk of inhibitor development across the class of products and therefore PRAC did not support the mentioning of these results in the SmPCs of corresponding medicinal products.

During the re-examination procedure, additional information from the SIPPET authors were submitted to PRAC. PRAC considered that the additional data submitted did not impact its conclusions on the results of the SIPPET studies and the limitations mentioned above.

Communication on risk of inhibitor development

With regards to the grounds claimed by LFB Biomedicaments regarding the level of information to be included in the product information and the communication on the risk of inhibitor development, PRAC considered that standardised information on the frequency for FVIII products in PUP and PTP should be reflected in section 4.8 of the SmPC, and only clinical studies providing relevant product-specific data (such as a specific frequency in PUP or PTP differing from the one stated in section 4.8 of the initial PRAC recommendation) should be reflected in the SmPC. This will ensure prescribers have access to robust and reliable information on the frequency of inhibitor development in the section 4.8 of the SmPC.

The PRAC maintained its conclusions that all human FVIII products carry a risk of inhibitor development, within the frequency of 'very common' and 'uncommon' for PUPs and PTPs respectively, and recommended that the SmPCs should be aligned with these frequencies, unless justified by robust product specific data, and that current references to study results on risk of inhibitor development in the product information of some FVIII products do not allow a definite conclusion for individual products and should therefore be deleted.

The above is without prejudice to the legal provisions laid down in Regulation (EC) No 1901/2006 ('Paediatric Regulation'), as acknowledged by the PRAC.

On the specific retrospective study for Factane, PRAC considered that the relevance of the results from the retrospective study is not demonstrated due to several limitations in the parameters used in the study and to some changes in clinical practices and therefore PRAC maintained its previous conclusion that these results are not suitable to be mentioned in the SmPC of Factane.

Overall, the PRAC maintains its conclusions that standardised information on the frequency for FVIII products in PUP and PTP should be reflected in section 4.8 of the SmPC, unless another frequency range for a specific medicinal product is demonstrated by robust clinical studies for which the results would be summarised in section 5.1.

Expert consultation

The PRAC consulted an ad hoc expert group on 3 August 2017 in particular to discuss whether the proposed changes to the product information, coupled with independent clinical guidance, provided an adequate level of information for prescribers and patients about the risk of inhibitor development associated with Factor VIII medicinal products. All data available, including all submitted data belonging to the SIPPET study, were considered by the expert group.

Overall, the expert group supported the PRAC initial conclusions that based on all available data no conclusion could be drawn on differences in the risk of inhibitor development between plasma derived and recombinant factor VIII medicines. The group also agreed that the proposed product information provides an adequate level of information to appropriately communicate to prescribers and patients about the risk of inhibitor development. No additional communication, on risk factors for inhibitor development beyond the product information or any additional risk minimisation measures was considered as necessary by the expert group.

The expert group also agreed that specific risk factors for inhibitor development should not be stated in the product information considering that there is no evidence to suggest prompt changes to the clinical management, e.g. additional monitoring of patients or choice of particular product.

The group also agreed that specific data about frequency of inhibitors for each product should not be included in the SmPC as the available studies are not adequately powered to draw precise conclusions on the absolute frequency for each product or on the relative frequency of inhibitors between products.

The experts also expressed the importance of adherence to the dosing and dose adjustment recommendations in section 4.2 of the SmPC and suggested some additional changes to the product information, in particular regarding the cut-off for the number of exposure days to separate PUPs from PTPs, the frequency of high-titre inhibitors and the current recommendation on switching treatment.

Finally, the experts welcomed initiatives to collect harmonised data through registries. Collaboration between academia, industry and regulators should be encouraged and data sharing agreements should be put in place.

4.2.3. Conclusion on the benefit-risk balance following the re-examination procedure

Further to the assessment by PRAC of the totality of the data submitted with regards to the risk of inhibitor development for the classes of recombinant and plasma derived FVIII products, as well as on the grounds submitted by LFB Biomedicaments, and on the views from two expert group meetings, the PRAC considered that:

- The SIPPET study was not designed to evaluate the risk of inhibitor development for individual products, and included a limited number of FVIII products. Due to heterogeneity across products, there is considerable uncertainty in extrapolating the findings of studies that have evaluated only class effects to individual products; and particularly to products (including more recently authorised products) which are not included in such studies.
- To date most studies evaluating a differential risk of inhibitor development between classes of FVIII products suffer from a variety of potential methodological limitations and based on the available data considered there is no clear and consistent evidence to suggest differences in relative risk between classes of FVIII products. Specifically, the current evidence suggests that all human FVIII products carry a risk of inhibitor development, within the frequency of 'very common' and 'uncommon' for PUPs and PTPs respectively and therefore the SmPCs of all factor VIII products should be aligned with these frequencies.
- Although the clinical studies for some individual products have identified limited numbers of cases of inhibitor development, these tend to be small studies with methodological limitations, or studies not adequately designed to evaluate this risk. Besides, the FVIII products are heterogeneous, and the plausibility of different rates of inhibitor development between individual products cannot be excluded. Therefore, references to studies where their robustness was not demonstrated should be removed from the SmPC of the concerned products.
- The results of any new clinical study providing relevant product-specific data (such as a specific frequency in PUP or PTP differing from the one stated in section 4.8 of the initial PRAC recommendation) should be reflected in the product information depending on their robustness (statistically and clinically compelling) in line with the SmPC guideline.

In conclusion, further to the initial assessment and the re-examination procedure, PRAC maintains its conclusion that the benefit-risk balance of the human plasma derived and recombinant coagulation

Factor VIII containing medicinal products remains favourable subject to the agreed changes to the product information (section 4.4, 4.8 and 5.1 of the SmPC).

5. Risk management

5.1. Amendments to the product information

The PRAC recommended the following updates of sections 4.4, 4.8 and 5.1 of the SmPC (and 2 and 4 of the Package Leaflet) for the FVIII products indicated for the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency).

The section 4.4 of the SmPC should be amended to include a warning on the clinical importance of monitoring patients for FVIII inhibitor development.

With regards to sections 4.8 and 5.1, reference to data from study results which do not allow a definite conclusion on the inhibitor risk for individual products should be removed. Frequencies for PUPs and PTPs should be respectively mentioned as 'very common' and 'uncommon', unless justified by product specific data. For products for which section 4.2 contains the following statement for PUPs: "*<Previously untreated patients. The safety and efficacy of {(Invented) name} in previously untreated patients have not yet been established. No data are available. >*", the above frequency for PUPs should not be implemented.

In relation to section 5.1, reference to inhibitor development studies in PUPs and PTPs should be deleted unless studies provide robust evidence of a product specific frequency of inhibitors in PUP. Statements on studies conducted in compliance with an agreed PIP are maintained.

The Package Leaflet was amended accordingly.

6. Grounds for Recommendation following the re-examination procedure

Whereas,

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data, for human plasma derived and recombinant coagulation factor VIII containing medicinal products (see Annex I and Annex A).
- The PRAC considered the totality of the data submitted with regards to the risk of inhibitor development for the classes of recombinant and plasma derived FVIII products, in previously untreated patients (PUPs). This included published literature (SIPPET study⁸), data generated in individual clinical trials and a range of observational studies submitted by the marketing authorisation holders, including the data generated in large multicentre cohort studies, data submitted by the national competent authorities of the EU Member States as well as responses provided by the Authors of the SIPPET study. PRAC also considered grounds submitted by LFB Biomedicaments as basis for their request for re-examination of the PRAC recommendation and the views of two experts meetings held on the 22 February 2017 and the 3 August 2017.
- The PRAC noted that the SIPPET study was not designed to evaluate the risk of inhibitor development for individual products, and included a limited number of FVIII products in total. Due to the heterogeneity across products, there is considerable uncertainty in extrapolating the findings of studies evaluating only class effects to individual products; and particularly to the products that are not included in such studies.
- The PRAC also considered that studies conducted to date suffer from a variety of methodological limitations and, on balance, there is no clear and consistent evidence to suggest differences in relative risks between FVIII product classes based on available data. Specifically, the findings from the SIPPET study, as well as those from the individual clinical trials and observational studies included in the MAH responses, are not sufficient to confirm any consistent statistically and clinically meaningful differences in inhibitor risk between rFVIII and pdFVIII product classes. Given these are heterogeneous products, this does not preclude individual products being associated with an increased risk of inhibitor development in ongoing or future PUP studies.
- The PRAC noted that the efficacy and safety of Factor VIII products as indicated in the treatment and prophylaxis of bleeding in patients with haemophilia A have been established. Based on the available data, the PRAC considered that SmPC updates for the FVIII products are warranted: section 4.4 should be amended to include a warning on the clinical importance of monitoring patients for FVIII inhibitor development. With regards to sections 4.8 and 5.1, the PRAC noted that several FVIII products currently include reference to data from study results which do not allow a definite conclusion on the inhibitor risk for individual products. Results of clinical studies not sufficiently robust (e.g. suffering from methodological limitations) should not be reflected in the product information on FVIII products. The PRAC recommended changes to the product information accordingly. Besides, as the evidence suggests that all human FVIII products carry a risk of inhibitor development, within the frequency of 'very common' and 'uncommon', for PUPs and PTPs respectively, the PRAC recommended that the

⁸ Peyvandi F, Mannucci PM, Garagiola I, et al. A Randomized Trial of Factor VIII and Neutralizing Antibodies in Hemophilia A. *The New England journal of medicine* 2016 May 26;374(21):2054-64

SmPCs of these products should be aligned with these frequencies unless justified by product specific data.

Therefore, the PRAC concluded that the benefit-risk balance of the human plasma derived and recombinant coagulation Factor VIII containing medicinal products remains favourable and recommended the variations to the terms of the marketing authorisations.