Annex II

Scientific conclusions

Scientific conclusions

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, severity of haemophilia, ethnicity, family history of inhibitor development and possibly HLA-DR (Human Leukocyte Antigen - antigen D Related) constitution.
- 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 or 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.

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 Medicine[1]. 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).

[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)

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 potential impact of the results of the SIPPET study on the marketing authorisations of relevant FVIII products and to issue a recommendation on whether these should be maintained, varied, suspended or revoked and whether any risk minimisation measures should be implemented. The referral focuses on the risk of inhibitor development in PUPs.

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.

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 study[2] 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).

The RODIN/Pednet study[3] 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).

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

[2] http://www.bloodjournal.org/content/109/11/4648.full.pdf
[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

(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.

Prior to the current referral, it was noted that PRAC had already considered the implications of the RODIN/Pednet, the UKHCDO and the FranceCoag studies for the EU marketing authorisations for FVIII products. In 2013, PRAC had concluded that the RODIN/Pednet findings 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. In 2016, PRAC had considered the findings of meta-analysis of all three studies (RODIN/Pednet, UKHCDO and FranceCoag studies), and again concluded 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 PUPs.

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 heterogenous 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, 2017[4]; Fischer K, 2015[5]) 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

[4] Iorio A, Barbara AM, Makris M, Fischer K, Castaman G, Catarino C, Gilman E, Kavakli K, Lambert T, Lassila R, Lissitchkov T, Mauser-Bunschoten E, Mingot-Castellano ME0, Ozdemir N1, Pabinger I, Parra R1, Pasi J, Peerlinck K, Rauch A6, Roussel-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.

[5] 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).

Ad hoc expert group meeting

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).

Discussion

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-authorised 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.

In view of the above, the PRAC recommended the following updates of sections 4.4, 4.8 and 5.1 of the SmPC as well as sections 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) as follows:

- 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 (in particular warning on the clinical consequences of low compared to high titre inhibitors).
- With regards to sections 4.8 and 5.1 of the SmPC, the PRAC noted that several FVIII products currently include reference to data from study results which do not allow for 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 such statements should be removed. The available data supports a frequency of FVIII inhibitor development within the frequency of 'very common' and 'uncommon', for PUPs and PTPs respectively, therefore the PRAC recommends that the SmPCs should be aligned with these frequencies 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, any reference to inhibitor development studies in PUPs and PTPs should be deleted unless the studies were conducted in compliance with a Paediatric Investigation Plan or the studies provide robust evidence of a frequency of inhibitors in PUP which is less than *'very common'* or for PTPs which is different from *'uncommon'* (as laid down in the attachments of the PRAC AR).

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.

Benefit –risk balance

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 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).

Re-examination procedure

Following the adoption of the PRAC recommendation during the May 2017 PRAC meeting, the MAH LFB Biomedicaments expressed their disagreement with the initial PRAC recommendation.

Given the detailed grounds provided by the MAH, the PRAC carried out a new assessment of the available data in the context of the re-examination.

PRAC discussion on grounds for re-examination

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. The findings from the SIPPET study, as well as those from the individual clinical trials and observational studies, are not sufficient to confirm any consistent statistically and clinically meaningful differences in inhibitor risk between the rFVIII and pdFVIII product classes.

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 meeting on some of the aspects that formed part of the detailed grounds submitted by LFB Biomedicaments.

Overall, the expert group supported the PRAC initial conclusions and 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 recommended.

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 emphasized that collaboration between academia, industry and regulators should be encouraged to collect harmonised data through registries.

PRAC conclusions

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).

The PRAC adopted a recommendation on 01 September 2017 which was then considered by the CHMP, in accordance with Article 107k of Directive 2001/83/EC.

Overall summary of the scientific evaluation by the PRAC

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 study[6]), 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 22 February and 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 heterogenous 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 methodolical

[6] 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

limitations) should not be reflected in the product information on FVIIII 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 product information 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.

CHMP opinion

Having reviewed the PRAC recommendation, the CHMP agrees with the PRAC overall conclusions and grounds for recommendation.