Annex IV

Scientific conclusions and grounds for variation to the terms of the marketing authorisations

Scientific conclusions

The CHMP considered the below PRAC recommendation dated 5 December 2013 with regards to the procedure under Article 20 of Regulation (EC) No 726/2004 for Kogenate Bayer and Helixate NexGen.

Overall summary of the scientific evaluation of Kogenate Bayer and Helixate NexGen

Kogenate Bayer and Helixate NexGen are full-length recombinant human antihaemophilic factor VIII (octocog alfa) produced in baby hamster kidney (BHK) cells. Kogenate Bayer/Helixate NexGen are indicated for treatment and prophylaxis of bleeding in patients with hemophilia A (congenital factor VIII deficiency). These products were approved in the European Union on 04 August 2000.

Development of inhibitors against FVIII is the most significant complication of replacement therapy for haemophilia A. These antibodies inactivate the pro-coagulant activity of FVIII and inhibit patients' response to FVIII replacement therapy which may result in life-threatening bleedings and sequelae.

In 2006, an EMA expert meeting[1] on FVIII products and inhibitor development concluded that there was a need to collect comparable clinical data on the immunogenicity of recombinant and plasma-derived FVIII products as a long-term objective. As a consequence, the marketing authorisation holder (MAH) for Kogenate Bayer and Helixate NexGen supported two EU registries:

- the RODIN (Research of Determinants of Inhibitor development)/PedNet registry; and
- the EUHASS (European Haemophilia Safety Surveillance System) registry.

Both registries were part of the risk management plan (RMP) of the respective products.

The results of the RODIN/PedNet study *(S. C. Gouw et al., N. Engl. J. Med. 368, 231 (2013))* were made available and seemed to suggest that Kogenate Bayer/Helixate NexGen were associated with an increased risk of inhibitor development in previously untreated patients (PUPs) when compared to another recombinant antihaemophilic factor VIII, after adjustment for confounding factors.

The Federal Institute for Vaccines and Biomedicines (Germany) informed the Commission on the findings on the 1st of March 2013. Therefore, the European Commission (EC) initiated a procedure under Article 20 of Regulation (EC) No 726/2004 and requested the Agency to assess available data and its impact on the benefit-risk balance of the medicinal products concerned and to give its opinion as to whether the marketing authorisations should be maintained, varied, suspended or revoked.

Clinical Safety

The MAH provided data on the above-mentioned observational studies with regards to the risk of inhibitor development in PUPs receiving FVIII products, including KOGENATE Bayer/Helixate NexGen. Updated results from the EUHASS registry were also provided.

The MAH also submitted data from four interventional clinical trials and six observational studies, which investigated the safety and efficacy of Kogenate Bayer/Helixate NexGen in haemophilia A patients, including studies 200021EU and 100074US in PUPs and minimally treated patients (MTPs). These studies were either sponsored or supported by the MAH.

[1] http://www.ema.europa.eu/docs/en_GB/document_library/Report/2009/11/WC500015512.pdf

Finally in support of the above mentioned clinical data, the MAH provided quality data with regards to the manufacturing process for Kogenate Bayer and Helixate Nexgen.

The efficacy of Kogenate Bayer/Helixate NexGen is recognised and the PRAC reviewed the data related to inhibitor development in PUPs and MTPs.

- Observational studies

RODIN/PedNet study

The objective of the RODIN/Pednet study was to examine the inhibitor development in PUPs with severe haemophilia A given recombinant or plasma-derived FVIII products. In this study, the incidence of inhibitor development ranged from 28.2% to 37.7% for all FVIII products. In patients given KOGENATE Bayer/Helixate NexGen, 64 out of 183 developed an inhibitor (37.7%), of which 40 had a high-titre inhibitor (25.2%).

Post-hoc analysis of the RODIN study showed that PUPs with severe haemophilia A given Kogenate Bayer were more likely to develop inhibitor than those given another recombinant antihaemophilic factor VIII (adjusted hazard ratio, 1.60; 95%-CI: 1.08 -2.37).

EUHASS study

The EUHASS study was established in 2008 as an adverse event reporting system for patients with inherited bleeding disorders, including Haemophilia A, in Europe.

The PRAC reviewed the preliminary 3-year data. In addition, the PRAC noted an update from the on-going EUHASS data, and results showed an inhibitor incidence for Kogenate Bayer and Helixate Nexgen comparable to other products: whereas no adjustment for known risk factors for inhibitor development could be performed due to the study design, the PRAC noted that the 95 % CIs of the point estimates of PUP inhibitor incidence were overlapping substantially between different products.

- MAH sponsored and supported clinical trials

Haemophilia centres in Western Europe and major haemophilia centres in North America enrolled a total of 60 PUPs/MTPs without pre-existing inhibitors in two studies (200021EU and 100074US).

These two interventional studies were carried out as prospective, uncontrolled trials, for treatment of bleeding episodes in 37 PUPs and 23 MTPs with residual FVIII:C < 2 IU/dl. Five out of 37 (14%) PUP and 4 out of 23 (17%) MTP patients treated with Helixate NexGen developed inhibitors within 20 ED (exposure days). Overall, 9 out of 60 (15%) developed inhibitors. One patient was lost to follow up and one patient developed a low-titre inhibitor during post study follow-up.

In one observational study, the incidence of inhibitor development in previously untreated patients with severe haemophilia A was 64/183 (37.7%) with Helixate NexGen (followed up to 75 exposure days).

- Quality data

In support of the above mentioned clinical data, the MAH provided information with regards to the manufacturing process (i.e. growth condition, purification) of Kogenate Bayer /Helixate Nexgen and discussed any change which took place since the studies 200021EU and 100074US.

In this context, the PRAC noted that Kogenate Bayer and Helixate Nexgen is potency labelled based on an one-stage clotting assay, in accordance with the approved quality documentation for the product, and not the chromogenic assay as per the European Pharmacopeia.

According to the MAH, since the Marketing Authorisations, 42 changes in the manufacturing process of KOGENATE Bayer have been introduced. Nine of these changes had a potential impact on inhibitor formation.

However, the data presented by the MAH indicate that there are no significant changes in the post-translational modifications, aggregation profile, specific activity or excipients since MA of Kogenate Bayer that might have increased the risk for inhibitor development over time.

The PRAC noted that all parameters were within specification and that there is no correlation between changes and inhibitor events.

- Conclusions

The PRAC considered results from the publication of the RODIN/PedNet study, the preliminary findings from the European Haemophilia Safety Surveillance System (EUHASS) registry and all available data submitted from clinical trials, observational studies, published literature as well as quality data for Kogenate Bayer and Helixate NexGen with regards to its potential risk of inhibitor development in previously untreated patients (PUPs) and minimally treated patients (MTPs).

The PRAC was of the view that the available data are consistent with the general experience that most inhibitors develop within the first 20 EDs and that the overall data does not provide evidence that factor VIII products differ from each other in terms of inhibitor development in PUPs.

In addition, upon request from the PRAC, the MAH provided analyses of the overall results on the observed inhibitor incidence in the light of the study design and patient selection. The PRAC noted that the Factor VIII gene mutation profile of these study population (in studies 200021EU and 100074US) reflects the typical distribution seen in patients with severe haemophilia A, indicating that there was no bias in patient recruitment.

In view of the above, the PRAC agreed that the current evidence does not confirm an increased risk of developing antibodies against Kogenate Bayer and Helixate NexGen when compared with other factor VIII products in PUPs with the bleeding disorder haemophilia A. However the PRAC considered that the frequency for inhibitor development in PUPs should be amended from *"common"* to *"very common"* in the section 4.8 of the SmPC and also recommended that the product information should be updated with results from the RODIN study as part of the routine risk minimisation activities.

The MAH will continue to support the RODIN/PedNet registry as well as the EUHASS registry, as per current obligations defined in the RMP, to further investigate individual risk factors for inhibitor development and risk mitigation in PUPs. No update of the RMP was considered necessary by the PRAC.

Benefit –risk balance

Having noted the above, the PRAC concluded that the benefit-risk balance of Kogenate Bayer and Helixate NexGen indicated as for the treatment and prophylaxis of bleeding in patients with hemophilia A (congenital factor VIII deficiency) remains favourable subject to the changes to the product information agreed.

Grounds for the variation to the terms of the marketing authorisations

Whereas

- The PRAC considered the procedure under Article 20 of Regulation (EC) No 726/2004 for Kogenate Bayer and Helixate NexGen.
- The PRAC considered the publication of the results of the RODIN/PedNet study, the preliminary findings from the European Haemophilia Safety Surveillance System (EUHASS) registry and all available data submitted from clinical trials, observational studies, published literature and quality data for Kogenate Bayer and Helixate NexGen with regards to its potential risk of inhibitor development in previously untreated patients (PUPs).
- The PRAC noted that the efficacy of Kogenate Bayer/Helixate NexGen is not questioned and, on the basis of the available data, concluded that the current results do not confirm an increased risk of developing antibodies against Kogenate Bayer and Helixate NexGen when compared with other factor VIII products in PUPs with the bleeding disorder haemophilia A.
- The PRAC considered though that the frequency for inhibitor development in PUPs should be amended from *"common"* to *"very common"* in the section 4.8 of the SmPC and also recommended that the product information should be updated to reflect the most recent results from the RODIN study.

The PRAC therefore concluded that the benefit-risk balance of Kogenate Bayer and Helixate NexGen 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.

CHMP opinion

Following the provisions under Article 20 of Regulation (EC) No 726/2004, the CHMP, having considered the PRAC recommendation dated 5 December 2013, is of the opinion that the marketing authorisations for Kogenate Bayer and Helixate NexGen should be varied as recommended by the PRAC. The amendments to the relevant sections of the Summary of Product Characteristics and package leaflet are set out in Annexes I and III.