



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee

Assessment report

Kogenate Bayer and Helixate NexGen

Procedures under Article 20 of Regulation (EC) No 726/2004

INN: octocog alfa

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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. Background information on the procedure

The scope of the review was to assess the impact of the publication of the results of the RODIN/PedNet registry and preliminary findings from the European Haemophilia Safety Surveillance System (EUHASS) registry on the benefit risk balance of Kogenate Bayer and Helixate NexGen.

In view of the above the European Commission initiated a procedure under Article 20 of Regulation (EC) No 726/2004. The European Commission requested the Agency on 04 March 2013 to assess the above concerns and its impact on the benefit/risk for Kogenate Bayer, and to give its opinion on measures necessary to ensure the safe and effective use of Kogenate Bayer, and on whether the marketing authorisation for this product should be maintained, varied, suspended or revoked.

After reviewing all the available data submitted by the MAH to address the concerns discussed, the PRAC adopted a recommendation on 05 December 2013.

2. Scientific discussion

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 meeting¹ 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.

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

2.1. Clinical aspects

Inhibitor development is an expected adverse event (AE) linked to the use of FVIII products. It occurs in about a third of previously untreated patients/minimally treated patients (PUPs/MTPs) with severe haemophilia A, most of whom are younger than two years of age. Inhibitors are the result of an allotypic immune response against exogenous FVIII () replacement therapy. The immune system on initial exposure to the infused clotting factor identifies it as a “foreign” protein. Inhibitor development is one of the main complications of treatment.

The reasons why about one third of patients develop inhibitors and the other two thirds of patients are seemingly tolerant to the foreign FVIII protein still continues to be investigated. What is known so far is that inhibitor development is a result of an intricate interplay of both genetic and environmental factors, with the causal FVIII gene mutation and other polymorphisms in immune response genes playing a major role.

Numerous trials have analysed the correlation of factors with the risk of inhibitors. The most compelling patient-related factors are haemophilia severity, FVIII gene mutations, and other genetic factors such as family history of inhibitors, and race or ethnicity.

The risk to develop an inhibitor is highest in the first 20 EDs (exposure days) to FVIII products, with >95% inhibitors detected by the 50th ED. Inhibitor development is lowest in patients who have received FVIII products for more than 150 EDs.

In clinical practice, inhibitors are detected in a variety of ways. Many times, diagnosis is linked to the routine screening of patients at their semi-annual or annual visits to the haemophilia treatment centres. Otherwise, the presence of inhibitors is suspected when there is inadequate response to therapeutic administration of FVIII for a bleeding event. By contrast, patients in clinical trials follow a scheduled timeline of screening where there is generally more frequent testing of inhibitors based on the clinical trial protocol.

The assay system used to diagnose inhibitors is susceptible to a high degree of variability, within a given laboratory, and between laboratories. The use of a central laboratory helps control for this issue, through rigorous assay validation and normalisation. A North American study showed an intra-laboratory coefficient of variation of 30 - 42% for inhibitor-positive samples (most North American laboratories use the Bethesda assay). The European Concerted Action on Thrombophilia Foundation inter-laboratory surveys of FVIII inhibitor assays since 2005, showed inter-laboratory coefficient of variation of 30% for Nijmegen and 40% for Bethesda assay. Currently, the Nijmegen-modified assay is often preferred because it is more sensitive and specific to low-titre inhibitors with less false-positive low-titre inhibitor results, and on average shows better performance and slightly lower intra-laboratory variation.

The occurrence of neutralising inhibitors in high titres is a severe complication. FVIII replacement may not be effective, and these patients may need “bypassing” therapy, acting in different pathways of the coagulation system, for management of their bleeding events. The efficacy of such “bypassing” therapy is generally not as efficient as regular FVIII substitution therapy in non-inhibitor patients and the haemostatic response to such “by-passing” treatment is often less predictable and furthermore the response cannot easily be monitored with laboratory tests.

Inhibitors are classified as high responding (high-titre), low responding (low-titre), and transient inhibitors.

1. High responding inhibitors are defined by a peak historical titre of ≥ 5 BU/mL, and a risk of anamnesis. In such instances, treatment of acute bleeds requires the use of “bypassing

agents” like recombinant Factor VIIa (rFVIIa) or activated prothrombin complex concentrates (aPCC). Long-term management involves consideration of long-term eradication of inhibitors (Immune Tolerance Induction or ITI).

2. Low responding inhibitors are defined by a peak historical titre <5 BU/mL, and a lack of anamnesis (increase in antibody titre on FVIII re-exposure). In the event of a bleeding event, these patients can be treated with a higher dose of the same FVIII. A low-titre inhibitor response does not require substantial dose adjustment and many low-titre inhibitors in the MAH trials disappeared while patients remained on unaltered dosing schedule.
3. Transient inhibitors are low-titre inhibitors that disappear spontaneously over a variable period of time, without any intervention. Such instances may go undetected if the patient is asymptomatic (no bleeding episode during the transient presence of inhibitors) or routine screening for inhibitors is not performed.

Long-term eradication of inhibitors is achieved with the use of ITI, in which patients are treated with either low dose or high dose of the same FVIII product that triggered the inhibitor (individualised therapy and physician choice), over a period of 1 to 3 years. ITI success rates (i.e., a BU/mL titre of “0” and a factor recovery of >66% of expected level after infusion of factor) of 53-79% have been reported from small cohort studies and retrospective national and international ITI registries. The successful patients are then transitioned over to prophylaxis or maintenance therapy with FVIII concentrates. ITI treatment is demanding and is associated with high costs.

Patients for whom the inhibitors cannot be eradicated after ITI are left with the option to treat bleeding episodes on-demand with bypassing agents such as rFVIIa (recombinant activated FVII) or aPCC (activated prothrombin complex concentrates). This therapy is demanding as it requires multiple injections to stop the bleeding and prophylactic therapy can only rarely be utilised in these patients.

2.2. 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.

An analysis of low and high titre inhibitor development in previously untreated patients (PUPs) from clinical trials and observational studies was provided by the MAH. The analysis considered the frequency of inhibitor development per patient and per exposure days, the method of inhibitor detection, the frequency of inhibitor testing, the length of follow-up in terms of exposure days, the known risk factors of patients included in clinical trials (such as severity of haemophilia, major FVIII gene defects, family history and non-Caucasian race, age at first treatment, intensity of early treatment and use of prophylaxis) and the bleeding episodes and clinical outcome associated with inhibitor development. The MAH also discussed the possible bias of studies (e.g. enrolment bias, centre effects).

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, the incidence of inhibitor development in PUPs with severe haemophilia A was 64/183 (37.7%) with Kogenate Bayer or Helixate NexGen (followed up to 75 exposure days), of which 40 had a high-titre inhibitor (25.2%).

The MAH received data from the RODIN study database. Only data from subjects starting treatment with Kogenate Bayer or Helixate NexGen were made available. While a data cut-off of May 2011 was used for the published RODIN analysis, the MAH received a more recent data with cut-off of Dec 2012, which included 7 additional patients and a longer follow-up time for patients who had not reached 75 EDs by May 2011. The updated data set shows cumulative incidence of inhibitor development rates of 30.6% for Helixate NexGen and 38.7% for KOGENATE Bayer. These divergent results for the same product within the same study illustrate the great variability in observed inhibitor rate seen in such observational studies.

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 antihemophilic 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. Currently, there are over 74 European haemophilia treatment centres from 26 European countries included according to the 3rd annual report.

The PRAC reviewed the preliminary 3-year data of the EUHASS study: a total of 14,467 patients had haemophilia A with 6210 severe haemophilia cases; 7617 of those patients were treated with factor concentrate during the 3rd observation year. A total of 1483 patients were treated with KOGENATE Bayer in the 3rd year, and 840 patients with Helixate NexGen. The incidence of inhibitor development within the first 50 EDs was 38.8% (95% CI: 27.1-51.5%) for KOGENATE Bayer and 32.0% (95% CI: 15.0-53.5%) for Helixate NexGen.

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. The preliminary results provided indicated that the incidence for inhibitor development within the first 50 EDs for Kogenate Bayer was 31% (95% CI: 22-41%) and 31% for Helixate NexGen (95% CI: 16-48%). 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.

Six studies were Post-Marketing Observational Studies (PMOS) where PUPs/MTPs were subsets of a larger study population. Two trials were interventional investigator sponsored landmark trials on regular prophylaxis in small children (Study JOS and Study CHPS).

Table 1: Prospective studies (interventional and non-interventional trials)

| Trial/Study, location in CTD | Phase | Design | Region | No. and Type of High Risk Patients | Overall No. of Patients (incl PTPs) | Number of Centres |
|--|--------------|---|----------------------|---|--|--------------------------|
| Prospective studies | | | | | | |
| Pooled studies 200021EU 100074US | III | interventional | Europe /USA | 37 PUPs /23 MTPs | 60 | 32 |
| KG0201EU | PMOS | non-interventional | Europe | 13 PUPs /12 MTPs | 220 | 55 |
| KG0201JP | PMOS | non-interventional | Japan | 17 PUPs /40 MTPs | 631 | 190 |
| KG0401TW | PMOS | non-interventional | Taiwan | 1 MTP | 70 | 8 |
| Bio Set - KG0402 | PMOS | non-interventional | Europe | 1 PUP 15 MTPs | 347 | 59 |
| CE1250_5001 | PMOS | non-interventional | Europe | PUP/MTP | 223 | - |
| KG0702/13405 | PMOS | non-interventional | Europe /North Africa | 3 PUPs /17 MTPs | 186 | 51 |
| 100458 JOS | | interventional investigator sponsored trial | USA | 64 MTPs | 64 | 14 |
| 100463 (CHPS) | | interventional investigator sponsored trial | Canada | 48 MTPs | 48 | 10 |

In the pooled MAH clinical trials (200021EU and 100074US), 60 PUPs or MTPs (defined as having ≤ 4 EDs) were exposed to Kogenate Bayer/Helixate NexGen. Nine of these 60 patients (15%; 95% CI: 7-27%) developed inhibitors. Of these, 6 of 60 patients (10%) had a peak inhibitor titre ≥ 5 BU (4 PUPs and 2 MTPs) and 3 of 60 patients (5%) had a titre <5 BU (1 PUP and 2 MTP). These patients were monitored for median number of 115 EDs and inhibitors were detected at a median time of 7 EDs. At the end of the trial, 4 of 5 patients who had not achieved 20 EDs ultimately achieved 20 EDs in a post-

study follow-up, and 1 of these patients developed a low-titre inhibitor. The fifth patient was lost to follow-up. Counting this patient as a potential inhibitor patient, the total inhibitor incidence would be increased to 18%.

In the MAH supported, investigator-sponsored, interventional JOS and CHPS trials, which included MTPs, the de-novo treatment emergent inhibitor rate was 8/64 (13%; 95% CI: 6-23%) and 5/48 (10%; 95% CI: 3-23%), respectively. In the JOS trial, 2 of the 8 observed inhibitors were high-titre inhibitors and occurred in the prophylaxis arm, while 6 were low-titre inhibitors, many of them of transient nature. In the CHPS trial, there were a comparable number of high and low-titre inhibitors. Median time to inhibitor development was 44 EDs and 17 EDs for JOS and CHPS, respectively.

In conclusion, five out of 37 (14%) PUP and 4 out of 23 (17%) MTP patients treated with Kogenate Bayer/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 Kogenate Bayer /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.

Similar to all pharmaceutical manufacturing, changes are a routine part of the product lifecycle management for biotech products. According to the MAH, since the Marketing Authorisations, 42 changes in the manufacturing process of KOGENATE Bayer were further evaluated. Nine of these changes had a potential impact on inhibitor formation and underwent additional analysis which consisted of analytical data review demonstrating product comparability through specific comparability assessments.

The MAH presented longitudinal data on post-translational modifications, aggregation profile, specific activity and co-purification of hamster host proteins, peptides and DNA. The MAH also clarified the biophysical or biochemical characteristics of Kogenate Bayer /Helixate Nexgen since the studies 200021EU and 100074US.

The data presented by the MAH indicate that biophysical and biochemical characteristics of Kogenate Bayer and Helixate Nexgen have not significantly changed since the initial MA and 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.

2.3. 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.

2.4. Product information

The PRAC recommended the amendments to be introduced in the summary of product characteristics (SmPC) and package leaflets, to reflect information on inhibitor development.

An updated product information for Kogenate Bayer /Helixate Nexgen with amendments to the wording in sections 4.4, 4.8 and 5.1, to reflect the results of the recently published observational RODIN/PedNet study (*S. C. Gouw et al., N. Engl. J. Med. 368, 231 (2013)*) was proposed by the MAH and endorsed by the PRAC.

Summary of product characteristics

Section 4.4 Undesirable effects

Cross-reference to 5.1 was made in that section with regards to hypersensitivity.

Section 4.8 Undesirable effects

This section was an updated in order to reflect the results of the recently published observational RODIN/PedNet study. The PRAC considered that the frequency for inhibitor development in PUPs should be amended (from “common” to “very common”).

Section 5.1 Pharmacodynamic properties

This section was revised to address hypersensitivity reactions (e.g. the paragraph on "*Hypersensitivity*" was moved from section 4.8 to section 5.1).

Package Leaflet

The corresponding sections of the package leaflet were amended accordingly.

3. Overall conclusion

Having noted the above, the CHMP 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.

4. Conclusion and grounds for the recommendation

Whereas

- The PRAC considered the procedure under Article 20 of Regulation (EC) No 726/2004 for Kogenate Bayer and Helixate NexGen (see annexes A).
- 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.