
Benefits continue to outweigh risks of using Kogenate Bayer/Helixate NexGen in previously untreated patients

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Information on Kogenate Bayer/Helixate NexGen

Kogenate Bayer and Helixate NexGen are identical medicines that marketed by the same company, Bayer Pharma AG. Kogenate Bayer is used in Malta. These products are known as second generation factor VIII products and are used to replace the factor VIII that is lacking in patients with haemophilia A, an inherited bleeding disorder.

Information about the safety concern

In March 2013, Medicines Authority circular P08/2013 described how a review of the benefits and risks of these products was started by the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) triggered by a publication from the RODIN/PedNet study¹. In the RODIN study about a third of all the children developed factor VIII inhibitors against their medicine, which reduces the benefit and makes bleeding more likely. This is a known risk for all factor VIII products but the authors of the study concluded that children given second generation full-length recombinant factor VIII products such as Kogenate Bayer were more likely to develop antibodies than those given a third generation recombinant product. An increase in inhibitor formation was not seen with other recombinant or plasma-derived factor VIII products.

In this review data from the European Haemophilia Safety and Surveillance System (EUHASS) was also reviewed as well as all current available data on the development of inhibitors in previously untreated patients. The PRAC decided that these data did not support a conclusion that Kogenate Bayer or Helixate NexGen were associated with an increased risk of developing factor VIII inhibitors compared with other products.

Although existing measures to minimise all the risks from using the products were considered adequate for both Kogenate Bayer and Helixate NexGen and should be continued, the PRAC recommended that the product information should be updated to reflect results from the RODIN study.

¹ 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.

Following the review, the PRACs recommendation was forwarded to the Committee on Human Medicinal Products. The CHMP considered the PRAC recommendations and agreed by consensus that they should be implemented.

The CHMP opinion will now be sent to the European Commission for the adoption of a legally binding decision

In Malta

Information to patients

- Haemophilia A is an inherited bleeding disorder in which there is a lack of factor VIII, which is needed for blood to clot normally. Untreated, the deficiency of factor VIII causes bleeding problems, including bleeding into joints, muscles, and internal organs that can lead to severe damage.
- Different forms of factor VIII are available as medicines to replace the missing clotting factor. A study in previously untreated patients with haemophilia A, which compared several of these, seemed to show that patients who were given Kogenate Bayer or Helixate NexGen (full-length second generation products) were more likely to develop antibodies than those given another factor VIII (a third generation product). These antibodies (factor VIII inhibitors) reduce the effectiveness of the medicine and make bleeding more likely.
- However, when all the evidence was assessed, including that from this study, there was not enough to support a genuine difference between the products. The benefits of treatment with Kogenate Bayer or Helixate NexGen continue to outweigh their risks in previously untreated patients.
- The products can continue to be used as recommended. However the product information will be updated to reflect the study results and ensure that healthcare professionals treating patients with haemophilia A are aware of them.

Information to healthcare professionals

- Despite concerns raised by the RODIN/PedNet study, overall the current evidence does not confirm that there is an increased risk of inhibitor development against full-length second generation factor VIII products such as Kogenate Bayer and Helixate NexGen.
- Kogenate Bayer and Helixate NexGen can continue to be prescribed and used as appropriate in the management of haemophilia A. Existing risk minimisation measures are considered adequate and should be continued.
- In addition, the product information for Kogenate Bayer and Helixate NexGen will be updated to reflect the results of the RODIN/PedNet study. The frequency of inhibitor development in previously untreated patients will be amended in line with the current evidence to 'very common'. These recommendations are based on the results of the

RODIN/PedNet study, preliminary findings from the European Haemophilia Safety Surveillance System (EUHASS) 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).

- Concerns about a potentially increased risk of factor VIII inhibitor development with full-length second generation factor VIII products were originally raised by the RODIN/PedNet study. This was an observational study which examined inhibitor development in previously untreated patients (PUPs) with severe haemophilia A who were given recombinant or plasma-derived factor VIII products. In this study, the incidence of inhibitor development ranged from 28.2% to 37.7% for all products. In patients given Kogenate Bayer/Helixate NexGen, the incidence of inhibitor development was 64/183 (37.7%) when followed for up to 75 exposure days, of whom 40 had a high-titre inhibitor (25.2%). Post-hoc analysis of the study showed that PUPs with severe haemophilia A given Kogenate Bayer were more likely to develop inhibitors than those given another recombinant antihaemophilic factor VIII (adjusted hazard ratio, 1.60; 95%-CI: 1.08 -2.37).
- However, when all the available data were considered, they were consistent with the general clinical experience that most inhibitors develop within the first 20 days of exposure and that factor VIII products did not differ from each other in terms of inhibitor development in PUPs.
- Quality data presented by the marketing authorisation holder also indicated that the biophysical and biochemical characteristics of Kogenate Bayer and Helixate Nexgen have not significantly changed since the initial marketing authorisation.

REFERENCES

¹ 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.

Reporting Adverse Drug Reactions

Healthcare professionals and patients are encouraged to maintain vigilance on all factor VIII inhibitors. Suspected Adverse Drug Reactions (side effects) may be reported using the Medicines Authority ADR form or online at <http://www.medicinesauthority.gov.mt/adrportal> or to the marketing authorisation holder or their local representatives.

Dr John Joseph Borg
Post-licensing Director

Healthcare professionals and patients are encouraged to regularly check the Medicines Authority website for product safety updates as these are issued on an ongoing basis.