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## CHMP confirms PRAC recommendations on Kogenate Bayer/Helixate NexGen

### Benefits continue to outweigh risks in previously untreated patients

On 20 December 2013 the European Medicines Agency's Committee on Human Medicinal Products (CHMP) endorsed previous recommendations which concluded that the benefits of Kogenate Bayer and Helixate NexGen, so-called second generation factor VIII products, continue to outweigh their risks in previously untreated patients with the bleeding disorder haemophilia A, but that the product information for these medicines should be amended. The recommendations, issued by the Agency's Pharmacovigilance Risk Assessment Committee (PRAC), resulted from a review of the medicines which did not confirm a higher risk of developing a type of antibody (factor VIII inhibitors) against these medicines when compared with other factor VIII products. Factor VIII is lacking in patients with haemophilia A and is given to them to allow their blood to clot normally.

The review by the PRAC was triggered by results from a study (the RODIN/PedNet study<sup>1</sup>) in previously untreated children with haemophilia A who were given different factor VIII products, as well as preliminary data from the European Haemophilia Safety and Surveillance System (EUHASS). About a third of all the children in the RODIN study 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 so-called second generation full-length recombinant factor VIII products such as Kogenate Bayer or Helixate NexGen 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.

After reviewing 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.

The CHMP considered the PRAC recommendations and agreed by consensus that they should be implemented. The CHMP opinion was then sent to the European Commission, which endorsed it and issued an EU-wide legally binding decision on 20 February 2014.

<sup>1</sup> 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.



## 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 has been 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 has been updated to reflect the results of the RODIN/PedNet study. The frequency of inhibitor development in previously untreated patients has been amended in line with the current evidence to 'very common'.

The Agency's 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 antihemophilic 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.

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### **More about the medicine**

Kogenate Bayer and Helixate NexGen are identical medicines that were authorised throughout the European Union (EU) on 4 August 2000. The marketing authorisation holder for both medicines is the same company, Bayer Pharma AG.

Kogenate Bayer and Helixate NexGen are known as second generation factor VIII products. They contain a form of factor VIII, octocog alfa, produced by a method known as 'recombinant DNA technology': it is made by cells into which a gene (DNA) has been introduced which makes them able to produce the clotting factor. The octocog alfa in these products has the same structure as natural factor VIII ('full-length'). They are used to replace the factor VIII that is lacking in patients with haemophilia A, an inherited bleeding disorder. Untreated, the deficiency of factor VIII in these patients causes bleeding problems, including bleeding into joints, muscles, and internal organs that can lead to severe damage.

Alternative products containing various forms of factor VIII are available and may be used similarly. These may be extracted from human blood ('plasma-derived'), produced as full-length recombinant products with varying degrees of exposure to other blood-derived proteins (first, second, or third generation), or may contain a shortened, but still active, recombinant form of the factor VIII molecule.

### **More about the procedure**

The review of Kogenate Bayer and Helixate NexGen was initiated on 5 March 2013 at the request of the European Commission, under Article 20 of Regulation (EC) No 726/2004.

A review of these data was first conducted by the Pharmacovigilance Risk Assessment Committee (PRAC). The PRAC recommendations were sent to the Committee for Medicinal Products for Human Use (CHMP), responsible for all questions concerning medicines for human use, which adopted the Agency's final opinion. The CHMP opinion was forwarded to the European Commission, which endorsed it and issued a final legally binding decision, valid across the EU, on 20 February 2014.

### **Contact our press officers**

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