



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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Pharmacovigilance Risk Assessment Committee (PRAC)

## Inhibitor development in previously untreated patients with severe haemophilia A treated with recombinant factor VIII products

The PRAC has concluded a review of a meta-analysis of data from three observational studies (1-3) assessing the risk of developing antibodies against recombinant factor VIII products in previously untreated patients (PUPs) with severe haemophilia A (factor VIII level < 1%). Inhibitor development is the most serious and challenging complication in the treatment of haemophilia A. Usually, inhibitor development, which is associated with a reduction in efficacy of haemostatic effect of factor VIII, occurs during the initial phase of factor VIII exposure (i.e. in young children).

The results of three large multicentre cohort studies (RODIN, UK Haemophilia Centre Doctors' Organisation (UKHCDO) and FranceCoag study groups) published in 2013 and 2014 indicated an increased risk for inhibitor development following treatment with Kogenate Bayer and Helixate NexGen in PUPs with severe haemophilia A. The PRAC had previously evaluated this issue following the publication of the RODIN study (1) in the framework of an Article 20 procedure in 2013, and had concluded that based on available evidence, the data did not support that Kogenate Bayer or Helixate NexGen were associated with an increased risk of developing factor VIII inhibitors compared with other products in PUPs.

In January 2015, following the publication of the UKHCDO and FranceCoag studies (2, 3), the PRAC agreed that a meta-analysis based on raw data from these studies, considered the most representative for this issue, may provide an opportunity to extend sample size and enable reliable comparisons among the different recombinant factor VIII products based on a common analysis model for all studies agreed upon by PRAC.

This meta-analysis was made possible through close collaboration with academia. The investigators of the studies provided the anonymised raw data in accordance with data protection rules for a rigorous analysis led by the PRAC rapporteur, enabling an additional independent evaluation to further assess the safety profile of these medicines.

The medicines studied in this meta-analysis include the centrally-authorized medicines octocog alfa (Advate, Helixate Nexgen / Kogenate Bayer) and moroctocog alfa (Refacto and Refacto AF), as well as another recombinant antihemophilic factor authorized at national level.

A total of 1,102 PUPs (481 RODIN, 293 FranceCoag and 328 UKHCDO) for whom data on exposure to recombinant factor VIII are available were included in this meta-analysis. The meta-analysis suggested



a trend towards an increase of high-titre inhibitor development and all inhibitor development with Kogenate Bayer compared to Advate. Overall, 147 out of 400 PUPs treated with Kogenate Bayer / Helixate Nexgen (37%) developed inhibitory antibodies, of which 88 (22%) had high-titre inhibitors. For Advate, a total of 100 out of 385 PUPs (26%) treated with the medicine developed inhibitors, of which 57 (15%) had high-titre inhibitors. The percentages are similar for the study period from 2004 onwards when both products were licensed in parallel. A similar trend was also observed for other recombinant factor VIII products. However, the results are even less pronounced due to sample size constraints.

Although the meta-analysis was well conducted, the PRAC noted several limitations including the possibility of residual confounding. Furthermore, the PRAC acknowledged that inhibitor development is multifactorial, where a number of parameters may have an impact on the incidence in PUPs, and that adjusting for all of these factors in the analyses may not be possible. The PRAC also noted that there has been no signal for a similar trend of increases in inhibitor incidences with Kogenate Bayer in previously treated patients in other studies, a population where the experience with this product is large.

The PRAC agreed that overall, 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 previously untreated patients. These conclusions are consistent with the previous conclusions drawn by the PRAC within the [review](#) carried out on Kogenate Bayer/Helixate NexGen in 2013.

The PRAC recommended that the marketing authorisation holders of recombinant coagulation factor VIII products should monitor published studies on drug inhibitor development with the aim of keeping the product information up to date.

Patients and parents or carers who have any questions should speak to their doctor or pharmacist.

## **References:**

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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.
2. Collins PW et al. Factor VIII brand and the incidence of factor VIII inhibitors in previously untreated UK children with severe haemophilia A, 2000-2011. *Blood*. 2014; 124(23): 3389-97.
3. Calvez T et al. Recombinant factor VIII products and inhibitor development in previously untreated boys with severe hemophilia A. *Blood*. 2014; 124(23): 3398-408.