NOTIFICATION TO THE PRAC/EMA SECRETARIAT OF A REFERRAL UNDER ARTICLE 31 OF DIRECTIVE 2001/83/EC
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This notification is a referral under Article 31 of Directive 2001/83/EC to the Pharmacovigilance Risk Assessment Committee (PRAC) made by the Paul-Ehrlich-Institut Germany

<Product Name (s) in the referring Member State if applicable> Procedure name *(if this is a class referral, replace the <INN containing medicinal products> by the therapeutic class)*	various human and recombinant coagulation factor VIII containing medicinal products
Active substance(s) *Please clarify name(s) and total number(s) of active substance(s)*	human coagulation factor VIII efmoroctocog alfa moroctocog alpha octocog alpha simoctocog alfa susoctocog alpha turoctocog alfa
Pharmaceutical form(s) *If all pharmaceutical forms are included, state 'All'.* *If not all pharmaceutical forms are included, please specify the ones included.*	*All*
Strength(s) *If all strengths are included, state 'All'.* *If not all strengths are included, please specify the ones included.*	*All*
Route of administration(s) *If all route of administrations are included, state 'All'.* *If not all route of administrations are included, please specify the ones included.*	*All*
<Applicants/Marketing Authorisation Holder(s)> <In the referring Member State>	Various

Background:

Today's standard treatment of congenital haemophilia (and acquired haemophilia A) is based on prophylactic or on-demand replacement therapy with coagulation factor VIII (FVIII), either with plasma derived or with recombinant FVIII products. FVIII products may be used for prophylactic and on demand treatment.

Inhibitor development (neutralizing antibodies against FVIII) in haemophilia A patients receiving FVIII products mostly occurs in previously untreated (PUPs) or minimally treated patients (MTPs) who are still within the first 50 -75 days of exposure to the treatment.
So far, it was assumed that inhibitor development occurs with both plasma-derived and recombinant FVIII concentrates, in up to one third of the patients with severe haemophilia A (< 1% Factor VIII) independent of the specific FVIII concentrate used.
Currently, treatment of severe haemophilia A patients is mainly started between the 1st and 2nd year of life when increasing mobility puts children at a progressively increasing risk for bleedings. Many children currently receive recombinant FVIII products as a preferred choice due to various reasons.

In 2013, the European Commission initiated a review under Article 20 of Regulation (EC) No 726/2004; this review was triggered by results of the RODIN/PedNet study which was conducted in previously untreated children with haemophilia A who were given different FVIII products, as well as by preliminary data from the European Haemophilia Safety and Surveillance System (EUHASS).

While the EUHASS data did not indicate a difference in risk between recombinant products , the results of the RODIN study concluded that children treated with the second generation full-length recombinant FVIII products (such as Kogenate Bayer or Helixate NexGen) were more likely to develop antibodies than those treated with a third generation recombinant FVIII product. An increase in inhibitor formation was not seen with other recombinant or plasma-derived FVIII products.

The PRAC reviewed available data under Article 20, and considered that these data did not support the conclusion that Kogenate Bayer or Helixate NexGen were associated with an increased risk of developing FVIII inhibitors compared to other recombinant products. The existing measures to minimise the risks related to the use of Kogenate Bayer and Helixate NexGen were considered adequate, but the PRAC recommended that the product information be updated to reflect the results from the RODIN study.

Furthermore, in April 2016, the PRAC, kindly supported by independent investigators, reviewed a meta-analysis of data from three observational studies, aiming to assess the risk of inhibitor development against particular recombinant FVIII products in previously untreated patients suffering from severe haemophilia A. The PRAC concluded that overall, the currently available evidence did not confirm that Kogenate Bayer/Helixate NexGen was associated with an increased risk of FVIII inhibitors compared to other recombinant FVIII products in previously untreated patients.

In May 2016, a scientific paper was published in the New England Journal of Medicine [1] providing new data for the development of neutralizing antibodies against FVIII in haemophilia A.

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[1] F. *Peyvandi et al. "A Randomized Trial of Factor VIII and Neutralizing Antibodies in Hemophilia A" N Engl J Med. 2016 May 26;374(21):2054-64)*

In conclusion, the Paul-Ehrlich-Institut considers that there is a Union interest:

- to assess the potential impact of the results of the study recently published in the N Engl J Med[1] on the marketing authorisations of FVIII products including risk minimisation measures.

Therefore, Germany considers that it is in the interest of the Union to refer the matter to the PRAC and requests that it gives its recommendation under Article 31 of Directive 2001/83/EC as to whether marketing authorisations of these products should be maintained, varied, suspended, or revoked.

As the request results from the evaluation of data resulting from pharmacovigilance activities, the opinion should be adopted by the Committee for Medicinal Products for Human Use on the basis of a recommendation of the Pharmacovigilance Risk Assessment Committee.

Signed Professor Klaus Cichutek
President Paul-Ehrlich-Institut

Langen, 6 July 2016

Date