



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

**Update of 9 June 2017:**

Following the PRAC's May 2017 recommendation, a marketing authorisation holder involved with this referral procedure has requested a re-examination. Upon receipt of the grounds for their request, the PRAC will start a re-examination, which is expected to conclude at the PRAC meeting of 29 August–1 September 2017.

5 May 2017  
EMA/153837/2017 rev.1

## PRAC concludes there is no clear and consistent evidence of a difference in inhibitor development between classes of factor VIII medicines

EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has completed its review of factor VIII medicines to evaluate the risk of developing inhibitors in patients with haemophilia A who have not previously been treated with these medicines. Having reviewed the available evidence, the PRAC concluded that there is no clear and consistent evidence of a difference in the incidence of inhibitor development between the two classes of factor VIII medicines: those derived from plasma and those made by recombinant DNA technology.

Factor VIII is needed for blood to clot normally and is lacking in patients with haemophilia A. Factor VIII products replace the missing factor VIII and help control bleeding. However the body may develop inhibitors as a reaction to these medicines, particularly in patients starting treatment for the first time. This can block the medicines' effect, so bleeding is no longer controlled.

The review was started following publication of the SIPPET study,<sup>1</sup> which concluded that inhibitors develop more frequently in patients receiving recombinant factor VIII medicines than in those receiving plasma-derived factor VIII medicines. The review also covered other relevant studies, including interventional clinical trials and observational studies.

The studies reviewed differed in their design, patient populations and findings, and the PRAC concluded that they did not provide clear evidence of a difference in the risk of inhibitor development between the two classes of factor VIII medicines.

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<sup>1</sup> Peyvandi F, Mannucci PM, Garagiola I, et al. A Randomized Trial of Factor VIII and Neutralizing Antibodies in Hemophilia A. *New England Journal of Medicine* 2016; 374(21):2054-64.



In addition, due to the different characteristics of individual products within the two classes, the PRAC considered that evaluation of the risk of inhibitor development should be at the product level instead of at the class level. The risk for each individual product will continue to be assessed as more evidence becomes available.

The PRAC recommended that the prescribing information should be updated to reflect the current evidence. The update should include, as appropriate, listing of development of inhibitors as a very common side effect in previously untreated patients and as an uncommon side effect in previously treated patients. The existing warning on inhibitor development should be amended to highlight that the presence of low levels of inhibitors poses less of a risk of severe bleeding than high levels.

The PRAC recommendation will now be sent to EMA's Committee for Medicinal Products for Human Use (CHMP) for the adoption of EMA's final opinion. Further details and information for patients and healthcare professionals will be published at the time of the CHMP opinion.

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### **More about the medicines**

The review covers all medicines containing factor VIII authorised in the European Union. Factor VIII is a clotting protein and these medicines are used to temporarily increase levels of this protein in patients with haemophilia A, helping to prevent and control bleeding.

Human plasma-derived factor VIII medicines are extracted from blood plasma. Recombinant factor VIII products, on the other hand, are produced by a method known as 'recombinant DNA technology': they are made by cells into which a gene (DNA) has been introduced to enable the cells to produce factor VIII. Factor VIII medicines include nationally authorised and centrally authorised products containing the active substances human coagulation factor VIII, efmoctocog alfa, moroctocog alfa, octocog alfa, simoctocog alfa, susoctocog alfa and turoctocog alfa.

### **More about the procedure**

The review of factor VIII medicines was initiated on 7 July 2016 at the request of the German medicines authority Paul-Ehrlich-Institute, under [Article 31 of Directive 2001/83/EC](#).

The review has been carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which has made a set of recommendations. The PRAC recommendations will now be sent to the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which will adopt the Agency's opinion. The final stage of the review procedure is the adoption by the European Commission of a legally binding decision applicable in all EU Member States.