15 September 2017
EMA/603417/2017

Factor VIII medicines: no clear and consistent evidence of difference in risk of inhibitor development between classes

EMA concludes review of human factor VIII medicines authorised in EU

The European Medicines Agency (EMA) has 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.

EMA's review was started following publication of the SIPPET study (1), which concluded that recombinant factor VIII medicines had a higher incidence of inhibitor development than plasma-derived medicines. The review also covered other relevant interventional clinical trials and observational studies. When all these data were examined, they did not provide clear evidence of a difference in risk of inhibitor development between the two classes of medicines.

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

Due to the different characteristics of individual products within the two classes, EMA concluded that the risk of inhibitor development should be evaluated individually for each medicine, regardless of class. The risk for each product will continue to be assessed as more evidence becomes available.

To reflect current knowledge, the prescribing information of factor VIII medicines will be updated to include, as appropriate, inhibitor development as a very common side effect in previously untreated patients, and as an uncommon side effect in previously treated patients. The warning on inhibitor development will be amended to state that low levels of inhibitors pose less risk of severe bleeding than high levels.

Information for patients

- Some patients with haemophilia A taking factor VIII medicines produce inhibitor proteins which stop these medicines from working properly.
- EMA looked at data to assess whether there is a difference in the risk of inhibitor development between factor VIII medicines manufactured with DNA technology and those extracted from human blood.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

- EMA concluded that there is no clear evidence of a difference in the risk of inhibitor development between the two classes of factor VIII medicines. Patients should therefore continue to use their factor VIII medicines as prescribed by the doctor.
- Package leaflets for factor VIII medicines will be updated as needed to say that inhibitor development is very common in patients with haemophilia A who have not previously had factor VIII medicines and is uncommon in patients who have already been treated with these medicines.
- Patients with any questions or concerns should contact their doctor or healthcare professional.

Information for healthcare professionals

- Current evidence does not support a conclusion of a difference in risk of inhibitor development between recombinant and plasma-derived factor VIII medicines and does not warrant any change in clinical practice.
- EMA's review of factor VIII medicines followed publication of the SIPPET study, a randomised clinical trial in which previously untreated patients with severe haemophilia A were treated with either blood-derived or recombinant factor VIII and development of inhibitors was assessed (1). The SIPPET investigators concluded that 'patients treated with plasma-derived factor VIII containing von Willebrand factor had a lower incidence of inhibitors than those treated with recombinant factor VIII.' This study and additional clinical trial and observational study data were examined in the review (including studies described in 2–5).
- The review concluded that the data did not show any statistically or clinically meaningful difference in inhibitor risk between factor VIII classes. The SIPPET study was designed to assess class effects and included a small number of factor VIII medicines, and the review considered that the results cannot be extrapolated to individual medicines, especially since many were not included in the study.
- The prescribing information for factor VIII products will be updated as appropriate to add inhibitor development as a very common side effect in previously untreated patients and as uncommon in previously treated patients. The warning on inhibitor development will be amended to state that low titres of inhibitors pose less risk of insufficient response than high titres.

References

The review looked at data from studies including:

1. Peyvandi F, Mannucci PM, Garagiola I et al. A Randomized Trial of Factor VIII and Neutralizing Antibodies in Hemophilia A. N Engl J Med (2016), 374:2054-64.
2. Gouw SC et al. Treatment-related risk factors of inhibitor development in previously untreated patients with hemophilia A: the CANAL cohort study. Blood (2007), 109:4648-54.
3. 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.
4. Iorio A et al. Natural history and clinical characteristics of inhibitors in previously treated haemophilia A patients: a case series. Haemophilia (2017), 23:255-63.
5. Fischer K et al. Inhibitor development in haemophilia according to concentrate. Four-year results from the European HAemophilia Safety Surveillance (EUHASS) project. Thromb Haemost (2015) 113:968-75.

Information on previous EMA reviews of factor VIII medicines can be found here:

EMA/108793/20144
http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Kogenate_Bayer_and_Helixate_NexGen/human_referral_prac_000022.jsp&mid=WC0b01ac05805c516f

EMA/PRAC/332348/2016 PRAC
http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2016/05/news_detail_002528.jsp&mid=WC0b01ac058004d5c1

More about the medicine

The review covers all medicines containing human 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.

Human factor VIII medicines include nationally authorised and centrally authorised products containing the active substances human coagulation factor VIII, efmoroctocog alfa, moroctocog alfa, octocog alfa, simoctocog 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 was first carried out by EMA's Pharmacovigilance Risk Assessment Committee (PRAC), the Committee responsible for the evaluation of safety issues for human medicines, which made a set of recommendations.

Following a request from a company concerned, the PRAC re-examined its initial recommendations. The PRAC's final recommendations were sent to the Committee for Medicinal Products for Human Use (CHMP), responsible for questions concerning medicines for human use, which has adopted the Agency's opinion.

The CHMP opinion will now be forwarded to the European Commission, which will issue a final legally binding decision applicable in all EU Member States in due course. 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.