European Medicines Agency
Post-Authorisation Evaluation of Medicines for Human Use

London, 31 July 2007
EMEA/310225/2007 Corr

Public statement
EMEA completes the review of recombinant factor VIII products[1] and inhibitor development

The European Medicines Agency (EMEA) has completed a review of data on recombinant factor VIII (FVIII) products and the risk of the development of inhibitors against these products.

Recombinant FVIII products are used for the prevention and treatment of bleeding in patients with haemophilia A. A major complication of treatment is poor bleeding control linked to the development of antibodies ('inhibitors') against FVIII. The risk of inhibitor development is higher in patients with severe haemophilia A than in patients with mild or moderate disease.

The occurrence of inhibitors in previously untreated patients is a natural response of the immune system to a foreign protein. However, the development of inhibitors in multiply transfused and stable, previously treated patients may be due to the characteristics of an individual recombinant FVIII product.

The outcome of a preliminary review of recombinant FVIII products and inhibitor development was published in October 2005[2]. This review highlighted the need for a workshop on FVIII and the risk of the development of inhibitors. An expert meeting took place in 2006 and a report has been published[3].

The final review of data collected since 2003 has now been completed. The conclusions are:

- On the basis of available data, it is not possible to estimate and compare the incidence of inhibitors between different recombinant FVIII products.
- There is a trend for recurrence of low-titre FVIII inhibitors after switching from one recombinant FVIII product to another in previously treated patients with more than 100 days of exposure. As only a few of these cases were known to have no inhibitors prior to switching, it is not possible to conclude whether this observation is related to a real recurrence or to closer monitoring of patients after a product switch.
- There is no need to change the established treatment schemes with recombinant FVIII products. However, a warning on inhibitor development is in the process of being added to section 4.4 of the summary of product characteristics for each recombinant FVIII product as follows:

  "Cases of recurrence of inhibitors (low-titre) have been observed after switching from one recombinant factor VIII product to another in previously treated patients with more than 100 exposure days who have a history of inhibitor development."
- To obtain reliable data on FVIII inhibitor incidence, all companies who hold a marketing authorisation for a recombinant FVIII product will be requested to undertake further investigation into this issue in accordance with the recommendations from the expert meeting, taking into account the ongoing revision of the Note for Guidance on Clinical Investigation of Recombinant factor VIII and IX Products[4].
- Co-operation between patients and haemophilia centres is important for detecting and recording details of inhibitor development in haemophilia patients. Healthcare professionals and patients can contribute to obtaining better data on the incidence of FVIII inhibitors, by participating in registries and post-marketing surveillance programmes conducted in accordance with the latest recommendations and guidance.

[1] Centrally-authorised recombinant Factor VIII in the European Union/European Economic Area are Advate, Kogenate Bayer/Helixate NexGen, Kogenate/Helixate and ReFacto. Recombinate is authorised through the mutual recognition procedure with the Netherlands acting as the Reference Member State.
[2] See http://www.emea.europa.eu/pdfs/human/press/pus/33131605en.pdf.
[3] See http://www.emea.europa.eu/pdfs/human/bpwg/12383506en.pdf.
[4] See http://www.emea.europa.eu/pdfs/human/bpwg/156199endraft.pdf

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 68
E-mail: mail@emea.europa,eu http://www.emea.europa.eu

- As plasma-derived FVIII products were not the focus of this review, no conclusion can be drawn on the occurrence of inhibitors associated with their use.

Patients should continue therapy and follow the recommendations of their doctors. If bleeding is not controlled with usual doses of a recombinant FVIII product, patients should consult their doctor immediately.

For further information, please contact:

Dr Panos Tsintis
Head of Sector Pharmacovigilance and Post-Authorisation
Safety and Efficacy of Medicines