European Medicines Agency
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EMEA Public Statement
Review of recombinant Factor VIII (FVIII) products* and inhibitor development

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Recombinant factor VIII (FVIII) products are used for prevention and treatment of bleeding in patients with haemophilia A.

One of the major complications of the treatment is a poor control of bleeding linked to the development of an antibody against factor VIII (also called an 'inhibitor'). 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 should be seen as a natural response of the immune system to a foreign protein. However, the development of inhibitors in multi-transfused and stable previously treated patients (PTPs) may be due to the characteristics of an individual FVIII product.

Before marketing authorisation, there is only limited information on inhibitor development in PTPs, and monitoring must be continued during the post authorisation phase, including post-marketing studies. This monitoring has revealed a higher number of cases of inhibitors in PTPs in recombinant FVIII products than would be expected from experience with plasma derived FVIII products. Because of this, the Committee for Medicinal Products for Human Use (CHMP) undertook a review of all currently authorised recombinant FVIII products to assess the risk of inhibitor development and to identify if there are differences in this risk between products.

The CHMP review of recombinant FVIII products included data from clinical trials, post-marketing studies (including on-going studies) and spontaneous reports. Inhibitors in PTPs have been documented for all recombinant FVIII products, although the true incidence of inhibitor development in PTPs cannot be obtained from post-marketing spontaneous reports.

It was not possible to reach definite conclusions on the incidence of inhibitors with each of the recombinant FVIII products, because of differences in study design of post marketing safety studies, case definitions, treatment regimes (e.g. for bleeding episodes), patient characteristics, methodology of the FVIII inhibitor assays and differences in the duration/follow-up of the studies.

On the basis of the reviewed data, the CHMP concluded furthermore that it is not possible to differentiate the risk of inhibitor development in PTPs among recombinant FVIII products. Currently it is also not known whether recombinant FVIII products are more immunogenic than plasma derived FVIII products.

Therefore, the EMEA wishes to inform health-care professionals and patients that:

- Inhibitors in PTPs have been reported for all recombinant FVIII products.
- On the basis of current data, it is not possible to quantify and compare the risk between recombinant FVIII products. Additional studies are needed.

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- Patients should continue therapy and follow the recommendations of their physicians.
- If bleeding is not controlled with usual doses, patients should consult their physician immediately.

A workshop is planned in the first quarter of 2006 to review current knowledge on FVIII products and inhibitor development. The EMEA will bring together a panel of recognised experts in this field, interested parties, patient associations and regulators.

The aim of the workshop will be to discuss standardization of requirements, definitions and methods used in pre-and post-marketing studies with PTPs and previously untreated patients for FVIII products, since these studies are an important tool for investigating the safety of such products.

The conclusions of this workshop will be made available on the EMEA website.

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