Factor VIII medicines: no clear and consistent evidence of difference in risk of inhibitor development between recombinant and plasma-derived products

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Information on Factor VIII medicinal product and inhibitor development

- Factor VIII is clotting factor needed for blood to clot normally. Patients with haemophilia A lack this clotting factor and are given factor VIII medicines to replace the missing factor VIII in order to help control and prevent bleeding.
- The body may develop inhibitors as a reaction to Factor VIII medicines, particularly when patients first start treatment. These inhibitors reduce the medicines' effect, so bleeding is no longer controlled in with haemophilia A.
- Two types of factor VIII medicines are used: **Human plasma-derived factor VIII medicines** and **recombinant factor VIII medicines.** Human plasma-derived factor VII medicines are extracted from blood plasma while recombinant factor VIII medicines are produced by a method known as 'recombinant DNA technology'. Recombinant factor VIII products are made by cells into which a gene (DNA) has been introduced to enable the cells to produce factor VIII.
- In the EU, Factor VIII medicines are authorised nationally and centrally and containing the active substances; human coagulation factor VIII, efmoroctocog alfa, moroctocog alfa, octocog alfa, simoctocog alfa and turoctocog alfa.

In Malta the following products are nationally authorised:

Active Ingredients	Product Name	Pharmaceutical Form	Classification	Authorisation Number	MAH/license holder
Human Coagulation Factor VIII 25 IU/ml, Human Von Willebrand Factor 26 IU/ml	Dried Factor VIII Fraction, Type 8Y	Powder and solvent for solution for injection	POM	MA049/00201	Bio Products Laboratory Limited
Human Coagulation Factor VIII 50 IU/ml, Human Von Willebrand Factor 38 IU/ml	Immunate 250 IU	Powder and solvent for solution for injection	POM	MA162/00701	Baxter AG
Human Coagulation Factor VIII 100 IU/ml, Human Von Willebrand Factor 75 IU/ml	Immunate 500 IU	Powder and solvent for solution for injection	POM	MA162/00702	Baxter AG
Human Coagulation Factor VIII 100 IU/ml, Human Von Willebrand Factor 75 IU/ml	Immunate 1000 IU	Powder and solvent for solution for injection	POM	MA162/00703	Baxter AG
Human Coagulation Factor VIII 50 IU/ml	Haemoctin SDH 250	Powder and solvent for solution for injection	POM	MA008/00101	Biotest Pharma GmbH

Sir Temi Żammit Buildings, Malta Life Sciences Park,
San Ġwann SĠN 3000, Malta
info.medicinesauthority@gov.mt | (+356) 23 439 000
www.medicinesauthority.gov.mt

Active Ingredients	Product Name	Pharmaceutical Form	Classification	Authorisation Number	MAH/license holder
Human Coagulation Factor VIII 50 IU/ml	Haemoctin SDH 500	Powder and solvent for solution for injection	POM	MA008/00102	Biotest Pharma GmbH
Human Coagulation Factor VIII 100 IU/ml	Haemoctin SDH 1000	Powder and solvent for solution for injection	POM	MA008/00103	Biotest Pharma GmbH
Human Coagulation Factor VIII 100 IU/ml, Human Von Willebrand Factor 172 IU/ml	Optivate 250 IU	Powder and solvent for solution for injection	POM	MA049/00901	Bio Products Laboratory Limited
Human Coagulation Factor VIII 100 IU/ml, Human Von Willebrand Factor 172 IU/ml	Optivate 500 IU	Powder and solvent for solution for injection	POM	MA049/00902	Bio Products Laboratory Limited
Human Coagulation Factor VIII 100 IU/ml, Human Von Willebrand Factor 172 IU/ml	Optivate 1000 IU	Powder and solvent for solution for injection	POM	MA049/00903	Bio Products Laboratory Limited
Human Coagulation Factor VIII 100 IU/ml	Emoclot	Powder and solvent for solution for infusion	POM	MA128/00202	Kedrion S.p.A
Human Coagulation Factor VIII 50 IU/ml	Octanate, 50 IU/ml	Powder and solvent for solution for injection	POM	MA754/00401	Octapharma (IP) Limited
Human Coagulation Factor VIII 100 IU/ml	Octanate, 100 IU/ml	Powder and solvent for solution for injection	POM	MA754/00402	Octapharma (IP) Limited
Human Coagulation Factor VIII 100 IU/ml	Octanate LV 100 IU/ml	Powder and solvent for solution for injection	POM	MA754/00403	Octapharma (IP) Limited
Human Coagulation Factor VIII 200 IU/ml	Octanate LV 200 IU/ml	Powder and solvent for solution for injection	POM	MA754/00404	Octapharma (IP) Limited
Octocog Alfa 25 IU/ml	Recombinate 250 IU	Powder and solvent for solution for injection	POM	MA1047/00601	Baxalta Innovations GmbH
Octocog Alfa 50 IU/ml	Recombinate 500IU	Powder and solvent for solution for injection	POM	MA1047/00602	Baxalta Innovations GmbH
Octocog Alfa 100 IU/ml	Recombinate 1000IU	Powder and solvent for solution for injection	POM	MA1047/00603	Baxalta Innovations GmbH

Information on the European Medicines Agency's review of Factor VIII medicines

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.

- The EMA's review was started following publication of the SIPPET study, which concluded that recombinant factor VIII medicines had a higher incidence of inhibitor development than plasma-derived factor VIII medicines.

- The EMA's review also covered other relevant interventional clinical trials and observational studies. When all data was examined, no clear evidence of a difference in risk of inhibitor development between the two classes of medicines was found.
- 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.

The EMA's opinion has been sent to the European Commission. A final legally binding decision applicable in all EU Member States has been issued by the European Commission.

In Malta

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. 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.
- 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.

For more information on review, including a list of reference, visit the European Medicines Agency's website

Advice 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.
- 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.

For more information on the review visit the European Medicines Agency's website. Previous safety circulars on factor VIII medicines can be found here.

Reporting Adverse Drug Reactions

Healthcare professionals and patients are encouraged to maintain vigilance on Factor VIII medicines. Suspected Adverse Drug Reactions (side effects) may be reported using the Medicines Authority Form (available from: **http://www.medicinesauthority.gov.mt/adrportal**), fill and send by postal mail to Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000 or send by email to **postlicensing.medicinesauthority@gov.mt** or to the marketing authorisation holder or their local representatives

Post-Licensing Directorate
Medicines Authority

Healthcare professionals and patients are encouraged to regularly check the Medicines Authority website for product safety updates as these are issued on an ongoing basis.

Feedback Form

The Medicines Authority thanks you for the time taken to read this safety circular. The dissemination of safety circulars is an important process whereby Regulatory Authorities can communicate important issues with respect to the safety of medicines, in order to protect and enhance public health

The Medicines Authority kindly invites your anonymous feedback about the regulatory action being communicated. This may be returned by folding this form (address side up), stapling the ends and then posting (no stamp required)

Feedback:

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Sir Temi Żammit Buildings

Malta Life Sciences Park

San Ġwann SĠN 3000