Annex III

Amendments to the product information

Note:

These amendments to the relevant sections of the product information are the outcome of the referral procedure.

The product information may be subsequently updated by the Member State competent authorities, in liaison with the reference Member State, as appropriate, in accordance with the procedures laid down in Chapter 4 of Title III of Directive 2001/83/EC.

Amendments to the product information

For all products listed in Annex I, the existing product information shall be amended (insertion, replacement or deletion of the text as appropriate) to reflect the agreed wording as provided below.

A. Summary of Product Characteristics

Section 4.4 - Special warnings and precautions for use

*(**[For all products listed in Annex I]** all existing information on inhibitor development should be replaced with the following)*

"Inhibitors

The formation of neutralising antibodies (inhibitors) to factor VIII is a known complication in the management of individuals with haemophilia A. These inhibitors are usually IgG immunoglobulins directed against the factor VIII procoagulant activity, which are quantified in Bethesda Units (BU) per ml of plasma using the modified assay. The risk of developing inhibitors is correlated to the severity of the disease as well as the exposure to factor VIII, this risk being highest within the first 20 exposure days. Rarely, inhibitors may develop after the first 100 exposure days.

Cases of recurrent inhibitor (low titre) have been observed after switching from one factor VIII product to another in previously treated patients with more than 100 exposure days who have a previous history of inhibitor development. Therefore, it is recommended to monitor all patients carefully for inhibitor occurrence following any product switch.

The clinical relevance of inhibitor development will depend on the titre of the inhibitor, with low titre inhibitors which are transiently present or remain consistently low titre posing less of a risk of insufficient clinical response than high titre inhibitors.
In general, all patients treated with coagulation factor VIII products should be carefully monitored for the development of inhibitors by appropriate clinical observations and laboratory tests. If the expected factor VIII activity plasma levels are not attained, or if bleeding is not controlled with an appropriate dose, testing for factor VIII inhibitor presence should be performed. In patients with high levels of inhibitor, factor VIII therapy may not be effective and other therapeutic options should be considered. Management of such patients should be directed by physicians with experience in the care of haemophilia and factor VIII inhibitors."

(….)

Section 4.8 – Undesirable effects

*(**[For <u>all</u> products listed in Annex I]** the wording should be revised as follows: all existing information on inhibitor development should be replaced with the following)*

(Any reference to inhibitor development studies in PUPs and PTPs in section 4.8 of the SmPC should be deleted.)

"Development of neutralising antibodies (inhibitors) may occur in patients with haemophilia A treated with factor VIII, including with <product name> < see section 5.1>. If such inhibitors occur, the condition will manifest itself as an insufficient clinical response. In such cases, it is recommended that a specialised haemophilia centre be contacted.

Tabulated list of adverse reactions

- *For <u>products where a study in PUPs is required but results are not yet available</u> (i.e. products not authorised in PUPs and for which section 4.2 contains the following statement for PUPs ("<Previously untreated patients. The safety and efficacy of {(Invented) name} in previously untreated patients have not yet been established. No data are available. >"), all existing information on inhibitor development should be replaced with the following:*

MedDRA Standard System Organ Class	*Adverse Reaction*	*Frequency*
Blood and lymphatic system disorders	*FVIII inhibition*	*Uncommon (PTPs) **

- *For the remaining products (i.e. products authorised in PUPs), all existing information on inhibitor development should be replaced with the following:*

MedDRA Standard System Organ Class	*Adverse Reaction*	*Frequency*
Blood and lymphatic system disorders	*FVIII inhibition*	*Uncommon (PTPs)** *Very common (PUPs)**

- *This footnote shall be implemented at the bottom of the table, as the use of acronym as applicable:*

** Frequency is based on studies with all FVIII products which included patients with severe haemophilia A. PTPs = previously-treated patients, PUPs = previously-untreated patients"*

(….)

Section 5.1 – Pharmacodynamic properties

(In accordance with the PRAC recommendation, existing relevant text in section 5.1 of the SmPC in relation to inhibitor frequency for **Recombinate** *should be deleted.)*

Recombinate:

~~*Inhibitor Development*~~
~~*The risk of developing inhibitors is correlated to the exposure to Antihaemophilic Factor VIII, this risk being highest within the first 20 exposure days. The reported incidence of inhibitory antibodies in patients with severe haemophilia A who are at high risk for inhibitors development (i.e. previously untreated patients) is estimated in studies to be 31% for Recombinate, which is within the reported range for plasma derived AHF.*~~

~~*In the PTPT clinical trial (PTP – previously treated patients), none of the 71 subjects developed a de novo FVIII antibody, but 22 of 72 evaluable per protocol PUPs (PUP – previously untreated patients) treated with Recombinate did develop FVIII antibodies and the above frequency was based on the PUP data. Of the 22, 10 were high titre (≥ 5 Bethesda Units) and 12 were low titre (< 5 Bethesda Units).*~~

B. Package leaflet

*[***[For all products listed in Annex I]** *the following texts should be added to or replace existing texts, as appropriate:]*

Section 2 - What you need to know before you <take> <use> X:

*[***[For all products listed in Annex I]** *the wording should be revised as follows:]*

"The formation of inhibitors (antibodies) is a known complication that can occur during treatment with all Factor VIII medicines. These inhibitors, especially at high levels, stop the treatment working properly and you or your child will be monitored carefully for the development of these inhibitors. If you or your child´s bleeding is not being controlled with <product name>, tell your doctor immediately."

(...)

Section 4 - Possible side effects:

- *[***[For products listed in Annex I for which a frequency for PUPs has been implemented in section 4.8 of the SmPC]** *the wording should be revised as follows:]*

"For children not previously treated with Factor VIII medicines, inhibitor antibodies (see section 2) may form very commonly (more than 1 in 10 patients); however patients who have received previous treatment with Factor VIII (more than 150 days of treatment) the risk is uncommon (less than 1 in 100 patients). If this happens you or your child´s medicines may stop working properly and you or your child may experience persistent bleeding. If this happens, you should contact your doctor immediately."

(...)

- *[***[For products listed in Annex I for which a frequency for PUPs has <u>not</u> been implemented in section 4.8 of the SmPC]** *the wording should be revised as follows:]*

"For patients who have received previous treatment with Factor VIII (more than 150 days of treatment) inhibitor antibodies (see section 2) may form uncommonly (less than 1 in 100 patients). If this happens your medicine may stop working properly and you may experience persistent bleeding. If this happens, you should contact your doctor immediately."

(...)