08 July 2016
EMA/PRAC/471535/2016

PRAC List of questions

To be addressed by the marketing authorisation holder(s) for human and recombinant coagulation factor VIII containing medicinal products

Referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data

Procedure number: EMEA/H/A-31/1448

Advate EMEA/H/C/0520/A31/0078
Elocta EMEA/H/C/3964/A31/0006
Helixate Nexgen EMEA/H/C/0276/A31/0178
Iblias EMEA/H/C/4147/A31/0002
Kogenate EMEA/H/C/0275/A31/0185
Kovaltry EMEA/H/C/3825/A31/0004
Novoeight EMEA/H/C/2719/A31/0014
Nuwiq EMEA/H/C/2813/A31/0015
Obizur EMEA/H/C/2792/A31/0003
Refacto AF EMEA/H/C/0232/A31/0134
Voncento EMEA/H/C/2493/A31/0022

Active substances: human coagulation factor VIII; efmoroctocog alfa; moroctocog alfa; octocog alfa; simoctocog alfa; susoctocog alfa; turoctocog alfa

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1. Background

Today's standard treatment of congenital haemophilia (and acquired haemophilia A) is based on prophylactic or on-demand replacement therapy with coagulation factor VIII (FVIII), either with plasma derived or with recombinant FVIII products. Principally both substance classes may be used for prophylactic treatment as well as for therapeutic treatment in case of spontaneous bleedings.

Inhibitor development in haemophilia A patients receiving FVIII products mostly occurs in previously untreated or minimally treated patients (PUPs), who are still within the first 50 days of exposure to the treatment.

Inhibitors are a treatment challenge for both blood-derived and recombinant factor VIII medicines, which are authorised in all Member states of the European Union. They are produced as a reaction to factor VIII products in some patients, particularly those starting treatment for the first time, and can block the effect of these medicines, causing loss of bleeding control.

So far, it was assumed that inhibitor development occurs with both plasma-derived or recombinant FVIII concentrates, with an average frequency of up to 30% independently of which factor concentrate is used.

Based on findings from a recent study, the investigators suggested that patients treated with plasma-derived factor VIII had a lower incidence of inhibitors than those treated with recombinant factor VIII products evaluated in this study[1].

Based on the above there is a Union interest to assess the potential impact of the results of the above study on the marketing authorisations of FVIII products including risk minimisation measures.

The review of factor VIII medicines has been initiated at the request of the Paul-Ehrlich-Institute, under Article 31 of Directive 2001/83/EC.

The review is being carried out by the Pharmacovigilance Risk Assessment Committee (PRAC), which will make a set of recommendations.

1 F. Peyvandi et al. "A Randomized Trial of Factor VIII and Neutralizing Antibodies in Hemophilia A" N Engl J Med. 2016 May 26;374(21):2054-64)

2. Questions

The marketing authorisation holders MAH(s) **of recombinant and plasma derived Factor VIII products** as per Annex I are requested to address the following questions:

Question 1

Please provide tabulated information on your currently authorised FVIII product (see annex). This should include:

a) a general description of the qualitative and quantitative composition, the current marketing status, as well as exposure data, from different Member states where the product is approved.

b) Information included in the summary of product characteristics (SmPC) and package leaflet regarding the risks of inhibitor formation, on contraindications, warnings and precautions, and undesirable effects. Please highlight the main differences between the product(s) information (PI) in the different EU member states.

Question 2

The MAH is requested to assess the potential impact of the results of the SIPPET study and other relevant safety data on inhibitor development in previously untreated patients on the marketing authorisation of your FVIII product including consideration of risk minimisation measures.

In discussing this issue, reference should be made to an analysis of low and high titre inhibitor development in previously untreated patients (PUPs) with severe haemophilia A (F8 < 1%) from (I) all clinical trials and (II) observational studies conducted by the MAH as well as by independent investigators should be provided. Possible limitations of the studies should be discussed.

The analysis should consider:

a) The frequency of inhibitor development taking into consideration the length of follow up in terms of exposure days

b) The method and frequency of inhibitor testing

c) The length of follow-up in terms of exposure days

e) Known environmental and genetic factors confounding for inhibitor development such as but not limited to severity of haemophilia A, major FVIII gene defects, ethnicity, age at first treatment, intensity of early treatment and use of prophylaxis.

f) Bleeding episodes and clinical outcome associated with inhibitor development

Annex

Question 1

a)

INN	Product name	Type of marketing authorisation	Marketing status	Sales figures	Estimated patient exposure[1]

[1.] Expressed in patient years and stratified by Member State, by indication and by age (<12 and 12-18). Reasonable efforts should be made to obtain this information; potential sources in addition to sales data include registries and healthcare databases. If no precise data is available an estimate can be provided.

b)

PI	SmPC	PL	Main differences in SmPCs/PLs between the different EU Member States
Inhibitor formation			
Contraindications			
Warnings and precautions			
Undesirable effects			