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REPORT OF EXPERT MEETING ON FACTOR VIII PRODUCTS AND INHIBITOR DEVELOPMENT

28 February 2006 –2 March 2006

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GLOSSARY

ADR	Adverse Drug Reaction
BPWP	Blood Products Working Party
BU	Bethesda Units
CDC	Centres for Disease Control and Prevention (US)
CHMP	Committee for Human Medicinal Products
CV	Coefficient of Variation
ED	Exposure Days
ELISA	Enzyme Linked ImmunoSorbent Assay
EMEA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration (US)
FIX	Blood Clotting Factor IX
FVIII	Blood Clotting Factor VIII
HCV	Hepatitis C Virus
HIV	Human Immunodeficiency Virus
ISTH	International Society of Thrombosis and Haemostasis
ITT	Immune tolerance therapy
IU	International Units
LA	Lupus Anticoagulants
MTP	Minimally Treated Patients
NHD	National Haemophilia Database
NIBSC	National Institute for Biological Standards and Control
PEDNET	European paediatric organisation for haemophilia management
PhVWP	Pharmacovigilance Working Party
PK	Pharmacokinetic
PUP	Previously Untreated Patient
PTP	Previously Treated Patient
RMP	Risk Management Plan
SD	Standard Deviation
SPC	Summary of Product Characteristics
TGF-β	Tissue Growth Factor β
vCJD	Variant Creutzfeldt-Jakob Disease
VWF	Von Willebrand Factor
WHO	World Health Organisation

SUMMARY

An EMEA expert meeting on FVIII products and inhibitor development was held on 28 February to 2 March 2006 to provide a forum to discuss the international standardisation and harmonisation of requirements for clinical studies on FVIII inhibitor development in haemophilia A patients. The long-term objective is to collect comparable clinical data on the immunogenicity of recombinant and plasma-derived FVIII products in future.

The expert meeting was divided into an open session, where haemophilia treaters, competent authorities from EU, US, Japan and Canada, representatives from the International Society for Thrombosis and Haemostasis (ISTH), the World Health Organisation (WHO), patient organisations and industry discussed clinical study requirements, and a restricted session, where EU competent authorities discussed the outcome of the meeting.

A number of issues were discussed relating to: current data on FVIII products and inhibitor development, FVIII inhibitor measurement, clinical relevance of FVIII inhibitor occurrence, clinical study design, registries, risk management, post-marketing studies and pharmacovigilance.

This report summarises the discussions held at the open sessions. Conclusions drawn from these discussions in the restricted session and at the Blood Products Working Party (BPWP) meetings in June and September 2006 are listed at the end of the report.

The outcome of these discussions will be taken into account in the revision of the Notes for Guidance on clinical investigation of human plasma-derived and recombinant FVIII and FIX products and the corresponding core Summaries of Product Characteristics (SPCs). In addition, on recommendation of the experts, the Committee for Human Medicinal Products (CHMP) has contacted the ISTH SSC Subcommittee for FVIII and FIX in June 2006 regarding two topics: the FVIII inhibitor assay and the development of common data sets for registries. The activities of the ISTH SSC Subcommittee in these two areas are complementary to the work of the CHMP/BPWP/Pharmacovigilance Working Party (PhVWP) and national competent authorities.

INTRODUCTION

The occurrence of an antibody against FVIII is a major clinical complication in haemophilia A treatment. The risk of inhibitor development is increased in patients with severe haemophilia A compared to moderate and mild disease. The occurrence of inhibitors in PUPs should be seen as an immune reaction to a foreign protein linked to patient specific factors such as to underlying clotting factor gene defect, genetic immunity disposition and pre-existing immunity, while the development of inhibitors in multi-transfused and stable PTPs may reflect neo-antigenicity of the product. In the early 1990's two clusters of inhibitors observed in PTPs treated with specific plasma-derived products showed that such neo-antigenicity is a real concern (Rosendaal et al. 1993; Peerlinck et al., 1993 and 1997). Since it is not known whether recombinant FVIII products carry an enhanced immunogenic risk and whether there are differences between recombinant products in their relative immunogenicity, CHMP initiated in 2003 a review of recombinant FVIII products and inhibitor development. (The EMEA/CHMP is responsible for recombinant FVIII products.)

This review, co-ordinated by the PhVWP in liaison with the BPWP, did not allow definitive conclusions on the incidence of inhibitor formation with recombinant FVIII products (EMEA public statement, 2005) based on the data collected in 2003 and 2004: Considering post-marketing spontaneous reports and all completed or ongoing post-marketing safety studies, it was not possible to finalise the comparison for all recombinant products due to differences in study design, 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 studies.

The CHMP recommendations arising from the EMEA review are:

- Pharmacovigilance planning is recommended for all recombinant FVIII products.
- There is a need to establish standardised requirements for pre- and post-marketing studies to ensure comparable safety data on inhibitor development in PUPs and PTPs treated with rFVIII products. Harmonisation at an international level is desirable to achieve this aim.
- The value of patient registries as a source of data on incidence of inhibitors should be further explored.

The purpose of the expert meeting on FVIII products and inhibitor development was to address these recommendations with the aim of collecting comparable clinical data on the immunogenicity of recombinant and plasma-derived FVIII products in future.

OPEN SESSION ON 28 FEBRUARY AND 01 MARCH 2006

SESSION 1

M. Haase, the chairperson of the BPWP, welcomed the participants and presented the rationale for convening the meeting.

SESSION 2 FVIII PRODUCTS AND INHIBITOR DEVELOPMENT – UPDATE

The scope of this session, chaired by P.M. Mannucci, was to introduce the subject of inhibitor development in haemophilia A patients. A general presentation on FVIII immunogenicity, followed by an update of the EMEA review of recombinant FVIII products, and a summary of the outcome of the 2005 French workshop on plasma-derived and recombinant FVIII were given.

Presentations

As a general introduction, P.M. Mannucci discussed the clinical importance of the occurrence of FVIII inhibitors in patients with severe haemophilia A. He stressed in particular the importance of inhibitor occurrence in PUPs, affecting 20-35% of these patients.

J.M. Saint-Remy highlighted the mechanisms of the FVIII immunogenicity. He discussed several patient-related and product–related factors predisposing to inhibitor formation. These include genetic disposition, pre-existing immunity, age at first treatment and ethnic origin of the patients, as well as FVIII mutation, glycosylation pattern, stabilisation and C2 aggregation of the FVIII preparation and its content of other plasma proteins (VWF, fibrinogen, fibronectin, TGF-β) as well as the route of administration.

B. Keller-Stanislawski presented the EMEA review on recombinant FVIII products and inhibitor development performed in 2003, 2004 and 2006, which assessed the data from clinical trials, post-marketing studies and spontaneous reports including the design of the studies and inhibitor assays. She identified several gaps in the comparison of different products: discrepancies in duration of the follow-up of the patients, dosing regimens and definitions of severe haemophilia, MTPs and PTPs, other patient characteristics, methods of inhibitor testing and the use of central versus local laboratories. The frequency of inhibitor development in PTPs and PUPs found in clinical trials prior to marketing authorisation is considered comparable for all products assessed. However, the post authorisation inhibitor incidence in PTPs cannot precisely be estimated from post-marketing spontaneous reports. Furthermore, risk management plans are considered essential for all recombinant FVIII products.

C. Ratignier reported on the outcome from the 2005 French workshop on "Development and management of inhibitors after treatment of haemophilia patients by recombinant or plasma-derived FVIII or IX:

Data indicating that the immunogenicity of plasma-derived FVIII and recombinant FVIII products may be different remain weak from a preclinical point of view. Transgenic animal models are needed to study the effect of the VWF component.

At the French workshop, available publications on FVIII inhibitor occurrence, which fulfilled defined inclusion criteria for evaluation, were assessed. As in the EMEA review on recombinant FVIII products, several issues made a comparative analysis of the studies difficult: The baseline FVIII level was variable or not well defined, the study designs and follow up times were variable, the number of patients in the studies was often low, and the risk factors for inhibitor development were only partly defined or not defined at all. The French workshop recommended a risk based approach for choice of FVIII product: If the risk of infection is considered as the most important issue, a recombinant FVIII product may be chosen for first line treatment. However, if the risk of inhibitors is considered as the most important issue, a plasma-derived FVIII product may be selected.