- *The change from one product to another might booster or silence an existing FVIII inhibitor. Currently there is insufficient follow-up on these cases. How should the follow-up after a switch to another recombinant FVIII or plasma-derived FVIII product be standardized?*

  I. Scharrer reported on the review of the risk for inhibitor development in PTPs when switching from plasma-derived to recombinant FVIII. In a series of 5 clinical trials with a total of 307 patients, one patient was found with a de novo, transient low titre inhibitor.

  For pharmacovigilance reporting, it appears important to obtain information about possible product switches before and after inhibitor detection.

  The participants agreed that possible ill effects of product switching could be extracted from registry data. The need for a European or international registry was emphasized.

  Nevertheless, no consensus on whether increased inhibitor testing should be implemented after a product switch was reached. Testing recommendations are different depending on the countries: in United Kingdom, every 6 months is recommended, while in France, after a product switch, inhibitor testing is recommended after 10-20 exposure days, and thereafter according to the patient status: in PTPs, inhibitor testing is performed upon each visit (one or two per year), while in PUPs with severe haemophilia, inhibitor testing is regularly performed every 5-10 until 50 ED, then every 3 months until 100 ED, then every 6-12 months.

5.4 DURATION AND FOLLOW UP, SAMPLE SIZE

Session 5.4, chaired by J. Ingerslev, addressed the duration, follow-up and sample size of clinical studies on inhibitor development. One presentation was followed by a round table discussion.

Presentation

J. Goudemand presented an overview of all available literature data on the scope of the session. While the occurrence of inhibitors is a relatively frequent and early event in PUPs, it is rare in PTPs. Therefore, duration and follow-up in clinical studies should be differently defined for PUPs and PTPs and should be long enough to detect the possible occurrence of inhibitors. In published studies, duration was monitored in exposure days and/or exposure months. Depending on the reasons for use (intensive treatment/ prophylaxis/ on demand), the same number of exposure days was accumulated in very different time periods and it is very likely that the patients were not exposed to the same inhibitor risk. J. Goudemand concluded that in PUP studies, all inhibitor risk factors as well as the exposure days or period of exposure should be documented until at least 50 cumulative ED. In PTPs inhibitor risk factors are probably more therapy-related than patient-related (intensity of previous exposure (>50, > 100, >150 ED), intensity of treatment, prophylaxis, mode of administration, product switch) and should be documented in a defined way. According to current practice in France, Italy and UK, the recommendation for the duration of inhibitor screening is a combination of ED and period of administration. J. Goudemand recommended monitoring clinically relevant inhibitors depending on titre and therapeutic consequences.

Discussion and Conclusions

Experts and regulators (J. Goudemand, C. Lee, R. Seitz, J. van der Bom) participated in the round table discussion. Three questions were addressed dealing with duration, follow-up and sample size required in clinical studies in order to enable proper assumptions on the FVIII inhibitor occurrence.

- *Duration and follow-up are important parameters to compare the FVIII inhibitor incidence in clinical studies. As published in literature, the FVIII inhibitor incidence observed over 2 or 4 years differs. How long should the duration and follow-up period be and how should it be defined, based on exposure days or years? Which clinical and laboratory parameters should be monitored and in which intervals (e.g. prophylaxis, treatment on-demand, consumption, number of bleedings, FVIII plasma level, inhibitor measurement) ?*

The requirements for follow-up of PUPs and PTPs as well as the requirements for pre-authorisation and post-marketing studies should be clearly distinguished.

The risk factors for inhibitor development in PUPs are well understood and experts agreed that PUPs should be monitored for at least 50 ED in clinical trials independently of the exposure period. On the other hand there is limited knowledge about risk factors for inhibitor development in PTPs. Experts suggested a longer follow-up period for PTPs. Considering that patients have the freedom of choice of product and treatment, they should be monitored as long as they are treated with one given product, e.g. through registries.

As previously mentioned in session 5.1, due to the small patient population, it is difficult to obtain firm evidence concerning immunogenicity of a product in pre-marketing clinical studies. According to the current CHMP note for guidance on clinical investigation of plasma-derived and recombinant FVIII products, pre-licensing immunogenicity data should be obtained in 50 PTPs to show that the product under evaluation does not exhibit any signs of abnormal immunogenicity compared to other products on the market. In this context, a follow-up of at least 50 ED seems to be relevant.

On the other hand, post-marketing studies can allow more freedom to request long-term data, notably regarding inhibitor development.

- *Should the number of exposure days to the product under which the FVIII inhibitor developed be given?*

  All the participants agreed to collect the number of exposure days to the product under which the FVIII inhibitor developed.

- *Concerning statistical evidence for a risk of inhibitor formation how should the sample size and observation period in clinical studies be defined to enable proper assumptions on the FVIII inhibitor incidence in PUPs and PTPs?*

  During the meeting, the FDA approach of pre-defining a cut-off for inhibitors was discussed. For the participants, it appears quite difficult to pre-define such a cut-off, based on pre-licensing data, which appear insufficient (see J. van der Bom presentation is Session 5.3). Any inhibitor case seen should be carefully analysed.

  From the presentation of J. van der Bom, it appears that randomised controlled trials to investigate inhibitor incidence are difficult to perform due to the high patient number required. Case control studies in PTPs could be a possible approach in order to get reliable and relevant data on inhibitor risk factors.

SESSION 6 REGISTRIES

Session 6 was chaired by C. Lee. The aim of this session was to discuss experiences gained with patient registries. For this purpose, 5 presentations were given followed by a plenary discussion.

C. Lee opened the session by highlighting the importance of epidemiological data on FVIII inhibitor formation. C. Lee mentioned that excellent data from national registries are already available in some countries. The survey of the existing registries provided by the EMEA was tabled for information. According to the survey, there are national registries in at least 10 Member States and registries are under construction in three Member States. The European paediatric organisation for haemophilia management (PEDNET) also includes a paediatric registry (www.pednet.nl). The International Society on Thrombosis and Haemostasis (ISTH) also has a database for FVIII Deficiency.

Presentations

The question of the potential benefits from introduction of a haemophilia patient registry and the link/exchange of data subsets between registries that could be provided was elaborated in the following presentations.

M. Soucie gave a presentation on the United States Pilot Study of Inhibitors in Haemophilia. The study is based on the Universal Data Collection (UDC) program, which monitors blood safety among recipients of blood products. Even though the UDC is not designed to study inhibitors, some related data are collected including demographics, bleeding frequency, inhibitor test results and all product brands used. In a preliminary study, 2.75 new inhibitor cases per 1000 person years were verified. No robust conclusion on the immunogenicity of different products could be made due to lack of statistical power. M. Soucie explained that, in the pilot post-marketing study, a data coordinator is employed to collect the factor exposure data and ensure the annual blood testing. Methodologies to collect required treatment and bleeding information are being explored. Inhibitor testing is performed in a centralised laboratory. Inhibitor testing is to be done annually and prior to any planned product switch. In addition complete gene sequencing in a central lab is planned. Inhibitor history, infusion logs and product details are collected using specific data collection forms, electronic data entry from the sites and by patient.
M. Soucie mentioned that, when fully implemented this approach will provide the benefits of large population monitoring that yields the most power for studying rare events, permits product choice and avoids random assignment to treatments, and facilitates the quality control of the study. He also elaborated on the need for international collaboration in this field to increase study power and diversity of products monitored.

C. Hay presented the results from the UK National Haemophilia Database (NHD), which was established in 1968. The database collects data to provide national statistics to promote improved healthcare for patients with bleeding disorders. The new diagnoses, deaths and patient demographics are reported. Annual treatment data, including products used, are available from the whole UK. Inhibitors and other adverse events are reported. A vCJD database has been recently developed. The system has a real-time adverse event reporting and quarterly on-line reminders for adverse events. C. Hay showed that the use of recombinant products has been increasing while the use of plasma-derived products has been decreasing from the late nineties. In haemophilia A patients, about 13% have less than 1BU inhibitors, less than 9 % have 1-5 BU inhibitors and only about 1 % have severe haemophilia with more than 5 BU inhibitors. In 1991-2001 28 % of patients changed products. The incidence of inhibitors is highest in the age group from 0 to 9 years of age (22 % in 1990-2003), and decreases remarkably with increasing age (0.5 % in patients aged from 10 to 19 years). The incidence increases again during the fifth and sixth decades. Data on the relative risk by product is not complete and the data between PTPs and PUPs are not directly comparable. The exposure data is available only for younger patients and the risk can be expressed only in terms of treatment years. C. Hay concluded that there seems to be no clear difference between the recombinant products and an improved dataset will be more informative in this regard.

B. Haschberger gave an overview on the building of a national register in Germany. According to the German Transfusion Act, the number of patients with haemophilia, with inhibitors, and the amount of product consumption figures are collected to obtain data concerning the supply situation. Since 1999 the data have been requested in paper questionnaires from the haemophilia treating physicians. The new German register is intended to provide an extended database to enable scientific evaluation to optimise the treatment of the haemophilia patients and to reduce unnecessary exposure and costs. It is also considered important to aggregate international data and harmonise definitions with other national registries. However, several challenges were faced. The German Transfusion Act foresees only the collection of summarised data, but a registry needs individual patient data. Due to the very high impact of data protection in Germany, it was important that the data would be securely anonymised and no list of patients would be generated. The registry will ensure that the data protection mechanism will enable long term follow-up, and diagnostic and therapy data will be included, as well as other extensions like adverse effects and infections. User-friendly software was considered essential for the motivation of the treating physicians. B.Haschberger stated that the German Haemophilia Register, which is planned to start by the end of 2006, is a joint activity of Paul Ehrlich Institute, German Ministry, the German scientific society GTH (Gesellschaft für Thrombose- und Hämostaseforschung), and the patient organisations DHG (Deutsche Hämophilie Gesellschaft) and IGH (Interessengemeinschaft Hämophiler).

H. K. Hartl, chairperson of the European Haemophilia Consortium (EHC) (44 National member organisations) gave the patients' perspective on registries. He pointed out that the number of national

registries in Europe and worldwide is low, even though the registries are vital in many aspects. The difference of registries vs. epidemiological surveys is often neglected and comparisons between the data not possible. In February 2006, the Western European national member organisations (NMO) Advocacy Initiative (a World Federation of Haemophilia (WFH) – EHC joint activity) considered the lack of national patient registries as number four in the list of threats for patients. The patients' organisations have been active in increasing the awareness of the disease at the political level and in promoting the concept of enhanced cooperation between people with haemophilia, the medical profession and health policy makers.

Discussion and Conclusions

W. Schramm opened the discussion by presenting preliminary data from an annual questionnaire from 1980 to 2005 on inhibitor prevalence in Germany.

The following question was addressed in the discussion of this session:

- *Which benefits would the introduction of a haemophilia patient registry and the link/exchange of data subsets provide?*

  Based on the presentations and discussions the following conclusions can be drawn:

  There is a clear need for registries. This comprehensive database on factor exposure enables scientific evaluation to optimise the treatment of haemophilia patients and identification of areas for research.

  International collaboration will be desirable in this area to increase study power and diversity of products monitored. The starting point could be a network of national registries. Common criteria for data collection are essential to ensure that data are compatible between national registries in order to allow pooling of anonymised data. It was proposed by experts to refer this topic for further consideration by the ISTH SSC Subcommittee on FVIII and FIX, who has already established a working party to develop a consensus minimum international data set for registries.

  The main challenges identified were resource issues, compliance issues with the data protection act in the EU, the definition of the data to be collected and combined, and the motivation of the treating physicians to collaborate. Public funding for registries was advocated. All physicians should be encouraged to participate at the national level by explaining the benefits of the registries.

SESSION 7 RISK MANAGEMENT, POST-MARKETING STUDIES AND PHARMACOVIGILANCE FOR FVIII PRODUCTS

The aim of this session chaired by C. Kreft Jais was to present the risk management plan procedure recently introduced in EU and to give the opportunity for the Industry to present its view on pharmacovigilance and risk management aspects for FVIII products.

Presentations

S. Blackburn presented the recent EU guideline on the Risk Management System and explained in which situations applicants should consider a Risk Management Plan. Briefly, the description of the risk management system is submitted in the form of a risk management plan. This plan consists of two parts: (I) the safety specifications and the pharmacovigilance plan; (II) the evaluation of the need for risk minimisation activities and, in addition, a risk minimisation plan, in case of the need for additional (i.e. non-routine) risk minimization activities.

J. Feingold and T. Steinbach presented Wyeth's approach on pharmacovigilance and risk management for FVIII inhibitors. Wyeth clearly advocates the use of registries and recommends a global comprehensive registry with participation of all MAHs, uniform data collection, and standardized laboratory assays.

G. Lemm presented the view of Bayer on clinical trials and post marketing surveillance. It is proposed to include large post-marketing studies with the general objective to evaluate long-term safety and efficacy, and with the specific objective to assess inhibitor risk and perform signal detection on a routine basis with a comprehensive follow-up program.

H. Ehrlich and B. Ewenstein presented Baxter's views on risk management and lessons learnt from registries. A post-marketing surveillance clinical program is considered of utmost importance to contribute to a reliable assessment of inhibitors. Baxter considers that prospective clinical trials in PTPs remain the best indicator of product-related immunogenicity. Baxter considers also that studies in immunologically naive patient populations are confounded by sample size and genetic /non-genetic risk factors. The need of standardisation of key variables (e.g. inhibitor assay, inhibitor definition, duration of observation, immune tolerance treatment methodology) is essential.

F. Bridey presented joint position statements of the International Plasma Fractionation Association (IPFA) members for pre- and post-marketing studies. The importance of defining the best conditions for clinical study design was highlighted to avoid statistical bias, to define the population (severity <1%), to monitor the mode of treatment, and define laboratory parameters. The example of a retrospective study in 104 exhaustive PUPs treated with one plasma-derived FVIII product, a pre-marketing study in PTPs and a post marketing study in PTPs was given.

C. Waller presented the Plasma Protein Therapeutic Association's (PPTA) view on RMP and pharmacovigilance for FVIII products. PPTA member companies do not anticipate any difficulties in implementing the EU guideline on risk management and are committed to work with the authorities on additional approaches for accurate determination of FVIII inhibitor frequencies. PTPs remain the patient population for the investigation of product related immunogenicity and pharmacovigilance is seen as the mainstay of post-licensing risk management. Non-interventional prospective data collection is supported for which a standardised protocol could be implemented in all countries. The FVIII inhibitor assay needs to be further standardised and ideally should be performed in some coordinated laboratories.

Discussion and Conclusions

A risk management plan should be considered for a new product or when a modification to an already approved product is introduced, taking the known genetic and environmental risk factors of inhibitor development into account as well as the severity of this rare serious adverse event.

The pharmacovigilance plan needs to clearly address the assessment of known risks (e.g. risk profile) and its standardized evaluation and the reporting of adverse reactions (ADRs; definition of inhibitors based on laboratory results, clinical signs and recovery and half-life). It needs to be highlighted that every inhibitor detected should be reported in the clinical trial setting and in pharmacovigilance surveillance. In this respect, the role of health care professionals is of utmost importance in order to help health authorities in assessment of pharmacovigilance.

The type I inhibitor is the clinically most dominant inhibitor in haemophilia A and the primary focus of haemophilia treaters. Nevertheless, there should also be alertness for type II inhibitors with their different kinetics. Type II inhibitors were induced under treatment with one modified double-virus inactivated plasma-derived FVIII product (SD + heat treatment at 63°C), which disappeared when patients were taken off the product (see also 5.1).

For a clear observation of rare ADRs, it was reiterated that registries would be an important tool to follow-up patients throughout the life-long course of disease and treatment.

CLOSURE OF OPEN SESSION

B. Ljungberg chaired this part of the meeting, in which the chairpersons from the single sessions gave final remarks.

In conclusion, inhibitor development in PTPs remains the focus of observation for pre-authorisation studies of new and modified recombinant and plasma-derived FVIII products. Standardized protocols for enrolment into the trials as well as for the conduct and evaluation of these studies are needed.

These protocols should contain defined risk factors and be based on ED rather than a specific time period (see previous experience in 5.1).

The need for a risk management plan for FVIII products was clearly identified by all stakeholders in order to enable the detection of inhibitors. The need for registries, large observational studies, and reporting of adverse events are important aspects in the pharmacovigilance setting.

However, from the discussion with the Experts, it was difficult to reach definite conclusions on the recommended design of post-marketing studies and, therefore, this would be further considered by CHMP's Blood Products Working Party and Pharmacovigilance Working Party.

RESTRICTED SESSION ON 2 MARCH 2006,

BPWP MEETINGS IN JUNE AND SEPTEMBER 2006,

RECOMMENDATION FOR THE REVISION OF THE

NOTES FOR GUIDANCE ON CLINICAL INVESTIGATION OF RECOMBINANT AND PLASMA-DERIVED FVIII PRODUCTS

Summary of Restricted Session and BPWP meetings

At the restricted session on 2 March 2006 and the BPWP meetings in June and September 2006, European regulatory experts discussed the views and consensus expressed by experts during the open session on 28 February and 1 March 2006 as follows:

In line with common clinical practice, the diagnosis of a FVIII inhibitor in a haemophilia A patient should primarily be based on clinical observations and be confirmed by FVIII inhibitor testing in the laboratory. The collaboration between clinical and laboratory staff is of most importance. For valid FVIII inhibitor results it is very desirable that also clinical laboratories working under field conditions participate in proficiency studies.

PTPs are defined as patients with more than 150 ED and PUPs as patients with no previous exposure to clotting factors. The suggested categorisation of patients in low-, intermediate- and high-risk groups will be further discussed during the revision of the guidelines on clinical investigation of plasma-derived and recombinant FVIII and FIX products.

From a regulatory point of view, health authorities must obtain sufficient assurance, before granting a marketing authorisation, that a new or modified product does not exhibit excessive immunogenicity. PTPs, who are clinically stable under regular replacement therapy, should be immunotolerant to FVIII, and an enhanced incidence of inhibitors would be unexpected and would be a signal of increased immunogenicity. Therefore for pre-licensing studies, PTPs appear to be the most relevant study population and should remain the target for the pre-marketing clinical studies. Standardised protocols for the enrolment into the trials, for the conduct of the inhibitor assays, especially for the non-interventional studies, and for the evaluation of the trial results are strongly requested.

The need for studying paediatric patients should take into account the Paediatric Regulation. Furthermore, the specific need for paediatric studies for new plasma-derived, new recombinant and modified products (e.g. pegylated) should be considered separately. PUPs are rare patients and BPWP members felt that data in PUPs should be collected when PUPs receive innovative products.

The risk profile is important for the evaluation of data and should be reflected as far as possible by the population studied. For pre-authorisation studies, preferably all known risk factors should be included in the investigation of the product and considered for the evaluation of data, e.g. genetics, age at onset of treatment, immunological situation strongly in correlation with age. According to the current status of scientific knowledge, this should be part of the protocols. For randomized trials there may be the need to match risk factors in study groups. To what extent these aspects may be appropriate for the post-marketing situation, will be further considered during the revision of the guidelines.

With regard to the small haemophilia A patient population, it is considered difficult to obtain firm evidence concerning immunogenicity of a new or modified FVIII product in pre-marketing clinical studies. Moreover, it appears difficult to set a predefined limit for the inhibitor incidence in PTPs solely on the basis of statistical considerations, without knowing the true incidence with plasma-derived and recombinant products on the market.

Considering these points, it is concluded, that the full immunogenicity evaluation of a given product could not be performed in the pre-marketing stage and it is important to foresee particularly efficient mechanisms of monitoring and pharmacovigilance for the post-licensing period. A complete

evaluation of product immunogenicity requires long-term data, which could only be obtained from post-authorisation setting, via post-marketing studies or registries. Post-marketing studies allow requesting of long-term data. An adequate design and standardization of post-marketing studies is of great importance, in order to collect relevant and reliable data to enable proper assumptions on FVIII inhibitor occurrence related to products. All these requirements should be reinforced in the revised guidance. Nevertheless, with an observational design, it will be difficult to stay on one given product, or one type of treatment, over an extended period.

It may not be evident to health care professionals when there has been a change to a specific product on the market through a modification in the manufacturing process. Therefore, in this context, it is of importance that MAHs commit to undertake appropriate inhibitor monitoring also after manufacturing changes. These requirements should be clearly highlighted in a risk management plan.

Also in post-marketing studies, the number of patients will be limited. Therefore, the establishment of national registries with harmonised data sets is strongly supported. In June 2006, as recommended during the expert meeting, CHMP contacted the ISTH SSC Subcommittee on FVIII and FIX products for collaboration on common data sets and also on FVIII inhibitor assay.

BPWP members noted that a new generation of recombinant FVIII products with longer half-life is in development and new experience on FVIII inhibitor development might be gained.

An additional point, which has been raised, concerns the meaningful information on inhibitors, which should be mentioned in the relevant sections of the SPC of a given product. Revision of the core SPC should clearly define what type of data should appear, in order to be as informative as possible for clinicians and patients with regards to the development of inhibitors.

Further Observations and Conclusions, as well as Recommendations for the Revision of the Notes for Guidance and core SPCs

In line with the consensus reached during the open session of the expert meeting, regulatory experts agreed with the following requirements and recommendations for the pre- and post-authorisation monitoring of inhibitor development in haemophilia A patients:

FVIII inhibitor assay

- The Nijmegen modification of the Bethesda assay is recommended for pre-authorisation studies and for post-marketing surveillance. Validated testing should be performed in a centralised laboratory for pre-licensing studies.
- Optimisation of the Nijmegen modification of the Bethesda assay should address the detection of type I, and also type II inhibitors.
- The participation of laboratories involved in clinical studies in proficiency and collaborative studies is essential.
- A threshold of ≥0.6 BU for the diagnosis of a low titre inhibitor was defined as well as a titre of ≥5 BU for a high titre inhibitor.
- A confirmatory test on a second, separately drawn sample should always be performed in a qualified laboratory. This second sample should be taken prior to any change of treatment and shortly after the previous positive test (within a month).
- For routine inhibitor testing, the inhibitor test should be performed when the plasma FVIII level has reached a pre-substitution nadir rather than at a specific time point. The inhibitor assay should be validated for the impact of residual FVIII on the test results.

Clinical conditions interfering with the FVIII inhibitor assay

- Presence of exogenous or endogenous FVIII: The interference of residual FVIII activity with the FVIII inhibitor assay can be circumvented by heating the sample in a validated step (e.g. one hour pre-treatment at 58°C).
- Lupus anticoagulant (LA): Differentiation of LA from FVIII inhibitors may be crucial, because of the different therapeutic interventions required. Two or more positive test results, particularly from assays with different designs, are more informative and more likely to differentiate LA from anti-FVIII inhibitors.

- Heparinised ports: In general, it is recommended for FVIII inhibitor testing to take blood from a vein and not from a port, as flushed heparin has an impact on FVIII inhibitor measurement.
- Chronic viral infections: Inhibitors have been detected in patients with chronic viral infections (e.g. HIV, HCV) during anti-viral therapy.

Clinical signs of inhibitor occurrence to be monitored

- PTP: Increased bleeding tendency, high consumption, lack of response or efficacy, decreased recovery, shortened half-life are indicative for an inhibitor in PTPs.
- Infants and young children: Poor response to treatment, including prophylaxis, is a useful clinical sign of inhibitor occurrence. High titre inhibitors may be indicated by an increased bleeding tendency (e.g. joint bleeds), while treated under a FVIII prophylaxis regimen. Effectiveness of treatment of a fresh joint bleed is measurable. Low titre inhibitors will probably not be detected under FVIII prophylaxis regimens. It is recommended to look at incremental recovery in a sample after infusion. Greatly reduced or no FVIII activity are indicative of an inhibitor. High consumption and increased bleeding are less reliable indicators in infants and young children.
- Careful consideration of all parameters is required, because some inhibitor patients do not bleed.

Clinical relevance of low titre inhibitors

Transient and low titre inhibitors might become a clinically relevant inhibitor in a PTP later in life. This indicates the importance of prolonged follow-up of patients. Such long-term data are much more difficult to collect, but are essential for pharmacovigilance assessment and registries. An additional difficulty in the interpretation of data is that FVIII inhibitor routine testing will often only be carried out in local laboratories rather than a central laboratory.

General recommendation for monitoring inhibitors

- Monitoring of inhibitor development should be started at the onset of treatment with a new or modified product in order to obtain solid baseline data.
- Regular laboratory measurements for inhibitors should be implemented in clinical studies. In addition, clinical signs suggesting inhibitor development should be defined and used to trigger investigations between the regular laboratory visits.
- Routine testing for inhibitors should be carried out on a regular basis. In particular, testing should be frequent in the early stages of replacement therapy. However, frequent sampling may prove difficult in young children.
- In order to identify product-related immunogenicity, all inhibitors should be documented and reported.
- Linking clinical and laboratory findings is very important.

Study population

- Product-related inhibitor development should be studied in PTPs pre-licensing.
- MTPs should not be included together with PUPs.

Definitions

Severe haemophilia A: FVIII baseline level of <1%. For pre-licensing studies, this definition (<1%) should be applied for PTP. In post-licensing studies, also patients with up to 2% baseline level may be included in the protocol for severe haemophilia A, when a separate statistical evaluation for <1% and <2% is provided.

PUP: Patients who never had exposure to clotting products, previous exposure to blood components is not excluded.

PTP: Patients at low risk, e.g. more than 150 ED.

MTP: not clearly defined and not useful concept.

Patient characteristics to be reported

Age
Age at time of first exposure to FVIII
General health status (infections (HIV, Hepatitis and other infections), vaccination)
Reason for treatment (e.g. bleeding, surgery)
Regimens and intensity of treatment (prophylaxis or on demand, in case of surgery continuous infusion or bolus injection, dosages and intervals)
ED (total, and to product under which treatment inhibitor developed)

Genetic risk factors:
Severity of haemophilia A
Gene mutation
Family history of inhibitors
Ethnicity

Mode of treatment

Prophylaxis vs. on demand treatment and continuous infusion
More data should be generated by post-marketing studies and pharmacovigilance reporting on inhibitors, in which information on prophylaxis vs. on demand treatment regimes and continuous infusion are being gathered.

Product switch
For pharmacovigilance reporting, it is important to get information about product switches before and after inhibitor detection. Respective data should be provided. The effects of product switching could also be investigated from registry data. The need for a harmonised data set in order to enable European or international evaluation is emphasized.

Also after changes to a specific product because of modifications in the manufacturing process, appropriate inhibitor monitoring should be undertaken. These requirements should be clearly highlighted in a risk management plan.

Duration and follow-up

Patients should be followed up for at least 50 ED, independently of the exposure period, in clinical studies performed prior to marketing authorisation. Long-term data can be obtained from post-authorisation setting, via post-marketing studies or registries (see below).

Sample size

Considering the small patient population, case control studies in PTPs could be a possible approach to get reliable and relevant data on risk factors for inhibitor incidence. In principle, any inhibitor case seen should be recorded.

Registries

A network of national registries with common criteria for data collection is desirable to ensure that data are compatible between national registries in order to allow pooling of anonymised data. This topic has been referred for further consideration to the ISTH SSC Subcommittee on FVIII and FIX.

Risk management, post-marketing studies and pharmacovigilance for FVIII products

The need for risk management plan, registries, large observational studies, and reporting of adverse events are important aspects in the pharmacovigilance setting for FVIII products.

REFERENCES

EMEA Public Statement - Review of recombinant Factor VIII (FVIII) products and inhibitor development. EMEA website: http://www.emea.eu.int/pdfs/human/press/pus/33131605en.pdf; 2005

Peerlinck et al.: A higher than expected incidence of factor VIII inhibitors in multitransfused haemophilia A patients treated with an intermediate purity pasteurized factor VIII concentrate. Thromb Haemost 69: 115; 1993

Peerlinck et al.: Factor VIII inhibitors in previously treated haemophilia A patients with a double virus-inactivated plasma derived factor VIII concentrate. Thromb Haemost 77: 88; 1997

Rosendaal et al: A sudden increase in Factor VIII inhibitor development in multitransfused haemophilia A patients in the Netherlands. Blood 81: 2180; 1993

LIST OF PARTICIPANTS

EXTERNAL EXPERTS

J. Astermark
University Hospital Malmö, Department for Hematology and Coagulation Disorders

G. Auerswald
Professor-Hess-Kinderklinik, Germany

J. Goudemand
Hôpital Cardiologique, Laboratoire d'Hématologie B, France

B. Haschberger
Paul-Ehrlich Institut, Germany

C. R.M. Hay
Manchester Haemophilia Comprehensive Care Centre, United Kingdom

J. Ingerslev
Haemophilia and Thrombosis Centre, Denmark

A. Kallas
University of Tartu, Institute of Cell and Molecular Biology, Estonia

R. Lassila
HUS, Department of Coagulation Disorders, Division of Hematology, Finland

C. Lee
United Kingdom

P.M. Mannucci
A. Bianchi Bonomi Hemophilia and Thrombosis Centre, Italy

P. Meijer
ECAT Foundation, The Netherlands

S. Raut
National Institute for Biological Standards and Control, United Kingdom

J-M. Saint-Remy
Centre for Molecular & Vascular Biology, University of Leuven, Belgium

I. Scharrer
Johannes Gutenberg-Universität Mainz, Germany

W. Schramm
Ludwig-Maximilian-Universität, Germany

J. van der Bom
Leiden University Medical Centre, The Netherlands

H. Verbruggen
Central Haematology Lab, UMC St Radboud, The Netherlands

REPRESENTATIVES FROM ACADEMIA

A. Gringeri
A. Bianchi Bonomi Centre, Italy

W. van Heerde
Central Laboratory for Haematology, Radboud University Nijmegen Medical Centre, The Netherlands

EXPERTS FROM ISTH

K. Mertens - Chair of ISTH SSC for FVIII and FIX
Utrecht Institute for Pharmaceutical Sciences, The Netherlands

BPWP MEMBERS, EXPERTS AND OBSERVERS

M. Haase – BPWP Chairman
Paul-Ehrlich Institut, Germany

D. Apele-Freimane
Zāļu valsts aģentūra, Latvia

N. Calvente Cestafe
Agenzia Española del Medicamento y Productos Sanitarios, Spain

E. Fabbri
Agenzia Italiana del Farmaco, Italy

C. Falção
Hospital Garcia de Orta Pragal, Portugal

B. Flores
Medicines and Healthcare products Regulatory Agency, United Kingdom

L. Gaydarova
Bulgarian Drug Agency

A. Hilger
Paul-Ehrlich Institut, Germany

P. Laitinen-Parkkonen
Lääkelaitos, Finland

B. Ljungberg
Läkemedelsverket, Sweden

E. Mavrokordatou
Ministry of Health, Cyprus

C. Rasmussen
Lægemiddelstyrelsen, Denmark

C. Ratignier
Agence Française de Sécurité Sanitaire des Produits de Santé, France

R. Seitz
Paul-Ehrlich Institut, Germany

M. van den Berg
Creveldkliniek, Utrecht University Medical Centre, The Netherlands

CHMP, PhVWP, BMWP, PAEDIATRICS WP MEMBERS AND OTHER EMEA EXPERTS

J. Dodt
Paul-Ehrlich Institut, Germany

B. Keller-Stanislawski
Paul-Ehrlich Institut, Germany

C. Kreft-Jais
Agence Française de Sécurité Sanitaire des Produits de Santé, France

D. Mentzer
Paul-Ehrlich Institut, Germany

F. Rotblat
Medicines and Healthcare products Regulatory Agency, United Kingdom

C. Schneider
Paul-Ehrlich Institut, Germany

D. Stenver
Lægemiddelstyrelsen, Denmark

R. Thorpe
National Institute for Biological Standards and Control, United Kingdom

M. van der Plas
Rijksinstituut voor Volkgezondheid en Milieu, The Netherlands

REPRESENTATIVES FROM EU AUTHORITIES

N. Grené-Lerouge
Agence Française de Sécurité Sanitaire des Produits de Santé, France

M. Hoefnagel
Rijksinstituut voor Volkgezondheid en Milieu, The Netherlands

N. Prieto Santos
Agenzia Española del Medicamento, Spain

REPRESENTATIVES FROM EUROPEAN HAEMOPHILIA CONSORTIUM / WORLD FEDERATION FOR HAEMOPHILIA

P. Giangrande
World Federation for Haemophilia (WFH), Oxford Haemophilia Centre, United Kingdom

H. Hartl
European Haemophilia Consortium (EHC), Austria

B. O'Mahoney
World Federation for Haemophilia (WFH)

U. Schlenkrich
European Haemophilia Consortium (EHC), Germany

REPRESENTATIVES FROM OTHER AUTHORITIES

C. Legare
Health Canada

J. Lozier
Food and Drug Administration, United States

C. Miller
Centers for Disease Control and Prevention, United States

H. Momose
National Institute of Infectious Disease, Japan

K. Nomura
Pharmaceutical and Medical Devices Agency, Japan

A. Padilla
World Health Organization, Switzerland

M. Soucie
Centers for Disease Control and Prevention, United States

K. Yamaguchi
National Institute of Infectious Disease, Japan

INDUSTRY REPRESENTATIVES

N. Bajwa
Bayer

E. Bastida
PPTA Industry (Grifols)

F. Bridey
IPFA Industry (LFB)

C. Dash
IPFA Industry (Bio Products Laboratory, UK)

H. Ehrlich
Baxter

T. Evers
International Plasma Fractionation Association (IPFA), The Netherlands

B. Ewenstein
Baxter

J. M. Feingold
Wyeth

K. Furuya
IPFA Industry (Japanese Red Cross, Japan)

E. Gorina
Bayer

S. Guazzini
PPTA Industry (Kedrion S.p.A.)

M. Gustafson
Plasma Protein Therapeutics Association (PPTA), Belgium

J. Lee
IPFA Industry (Bio Products Laboratory, UK)

INDUSTRY REPRESENTATIVES (continues)

G. Lemm
Bayer

J. Lindner
PPTA Industry (Biotest AG)

S. Renlund
Biovitrum AB, Sweden

F. Rossi
IPFA Industry (LFB)

D. A. Roth
Wyeth

T. Steinbach
Wyeth

P. Strengers
IPFA Industry (Sanquin)

T. Suiter
PPTA Industry (ZLB Behrng)

L. von Bonsdorff
IPFA Industry (Sanquin)

I. von Hoegen
Plasma Protein Therapeutics Association (PPTA), Belgium

C. Waller
Plasma Protein Therapeutics Association (PPTA), Belgium

O. Walter
PPTA Industry (Octapharma)

J. Weber
Bayer

EMEA SECRETARIAT

B. Neugebauer

C. Drai

K. Balzan

S. Blackburn

J. Childs

S. Domingo

X. Kurz

G. Silvester

P. Tsintis

L. Svobodova