London, 24 January 2008
Doc. Ref. EMEA/CHMP/BPWP/361857/2006

REPORT OF EMEA EXPERT MEETING ON THE REVISION OF THE CORE SPC AND NOTE FOR GUIDANCE FOR HUMAN NORMAL IMMUNOGLOBULIN FOR INTRAVENOUS ADMINISTRATION (IVIg)

5-6 July 2006

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GLOSSARY

ABMT	Allogeneic bone marrow transplantation
BPWP	Blood Products Working Party
CHMP	Committee for Medicinal Products for Human Use
CIDP	Chronic inflammatory demyelinating polyradiculoneuropathy
CLL	Chronic lymphocytic leukaemia
cSPC	Core Summary of Product Characteristics
DM	Dermatomyositis
GBS	Guillain Barré Syndrome
GvHD	Graft-versus-Host disease
HSCT	Allogeneic hematopoietic stem cell transplantation
ITP	Idiopathic (autoimmune) thrombocytopenic purpura
IVIg	Human Normal Immunoglobulin for Intravenous Administration
MA	Marketing Authorisation
MAA	Marketing Authorisation Application
MG	Myasthenia gravis
MM	Multiple myeloma
MMN	Multifocal motor neuropathy
NfG	Note for Guidance
Ph. Eur.	European Pharmacopoeia
PID	Primary immunodeficiency
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PM	Polymyositis
QOL	Quality of life
RMP	Risk Management Plan
s-IBM	Sporadic inclusion body myositis
SPC	Summary of Product Characteristics
VOD	Veno-occlusive disease

SUMMARY

The objective of the meeting was to assess information from the literature and from experts in the various medical fields where intravenous immunoglobulin products (IVIgs) are applied in order to adequately update the CHMP core SPC and Guideline for IVIg to the state-of-the-art clinical knowledge.

In an introductory session the relevant regulatory framework was portrayed with a particular focus on the impact of the upcoming paediatric regulation, the possibility of harmonisation with US Guidance, the significance of the new Small Populations Guideline for the evaluation of rare disorders in which IVIgs are currently used off-label (especially in neuroimmunological disorders) and the relevance of the ITP model for the immunomodulatory actions of IVIgs.

The beginning of the second session was devoted to the current understanding of the immunopathogenesis of autoimmune illnesses and the role of IVIgs within this complex set of diseases. The main part of this session focused on the so-called "established indications" and what were considered necessary alterations in light of recent research, literature review and other guidance documents. The Parisian approach of continuous evaluation and hierarchical structuring of a wide variety of indications was presented.

Primary immunodeficiencies (PIDs) are thought to be widely under-diagnosed, possibly as much as 95% worldwide, though the under-diagnosis rate in Europe is lower, probably ranging from 20-80%. Thus, it is essential to implement standardized diagnostic criteria and tools, assess real prevalence and incidence and judge the impact of PID on public health. Valuable information on PID should be retrieved from the newly established ESID registry. The licensing procedure of IVIg products for PID in the US was expanded on; precise statistical models for a trial design were presented. Subgroups of hypo- and agammaglobulinemias were described. With regard to the dosing of PID, most infections can be controlled by trough levels of 5.5 – 6.5 g/l. However, when comparing trough levels and infections rates, an additional benefit can be seen in trough levels of 6 – 9 g/l and doses should be adjusted for individual patients for infection prophylaxis to maintain long-term pulmonary function.

For IVIg use in chronic lymphocytic leukaemia (CLL) it was suggested to take on board the wording of the British Committee for Standards in Haematology: CLL patients with hypogammaglobulinemia and recurrent bacterial infections, especially those in whom prophylactic antibiotics have failed. The question of the correct dose to prevent all bacterial infections is still unresolved and is probably patient dependent. For multiple myeloma (MM), the suggested SPC wording is: Plateau phase MM patients with hypogammaglobulinemia and recurrent bacterial infections who have failed to respond to pneumococcal immunisation.

For allogeneic hematopoietic stem cell transplantation (HSCT) it was concluded that IVIgs should not be used for prophylactic treatment in conventional myeloablative HSCT, as there is no benefit on survival and the risk of veno-occlusive disease is increased. However, IVIg can be given with benefit in a prophylactic setting for secondary B-Cell deficiency (IgG < 4g/l) after HSCT. Other indications (GvHD, viral complications) show no overall benefit from IVIg treatment. The role of IVIg in the new HSCT strategies remains to be determined.

Most safety issues are currently covered by the SPC but a few additional points were identified for the current update.

The third session (Day 2 Session 1) focused on IVIg administration in neuroimmunological disorders. The conclusions on IVIg treatment in multifocal motor neuropathy (MMN) from the Cochrane Review are that a statistically significant effect on muscle strength can be seen, approximately one third of the patients have > 12 months remission, however, there is no significant effect on disability.

For chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), IVIg proved to be superior to placebo (4 trials, 4 different brands of IVIg were used) and showed similar efficacy to plasma exchange and prednisolone. These comparative studies had some methodological issues.

For moderate or severe chronic myasthenia gravis (MG), the data were too limited to draw any precise conclusions. For treating MG exacerbations, one randomised controlled trial of IVIg versus plasma exchange showed similar responses but lower complications rates with IVIg.

The data for the treatment of dermatomyositis with IVIg is limited to one albeit positive trial.

In the paediatric field, current core SPC recommendations for Kawasaki disease were thought to be adequate. It was proposed to modify the indication for children with congenital AIDs to include adolescents and to specify that it is for use in patients with recurrent bacterial infections. Currently data for the use of IVIg in neonatal sepsis is not sufficient; results of a large-scale trial will be available in 2008. Extrapolation from adult data for the use of IVIg for paediatric CIDP, MG and GBS was considered appropriate. In general the experts felt that no new efficacy data is required for the paediatric use of IVIg for the "established indications". There may be a need for more data on adverse events and posology issues.

Even though the randomised controlled trial as a method for clinical trial was acknowledged to provide most reliable data, other approaches were also recommended to be taken into account when generating data for the very rare conditions, including databases and patient registries, and post-authorisation studies.

The meeting had identified areas where IVIg is being used with promising results. Where indications are not taken into the core SPC as "established indications", applicants would need to submit sufficient data to support a MAA, making use of the available regulatory tools.

INTRODUCTION

The current Note for Guidance (NfG) on the Clinical Investigation of Human Normal Immunoglobulin for Intravenous Administration (IVIg) (CPMP/BPWG/388/95 rev.1) and the Core Summary of Product Characteristics (cSPC) for Human Normal Immunoglobulin for Intravenous Administration (IVIg) (CPMP/BPWG/859/95 rev. 2) have been in operation since December 2000. Medical knowledge and treatment regimens in the areas covered by the NfG and cSPC are in a state of continual development. Especially the past 5-10 years have seen many changes e.g. in the therapy of AIDS, in the use of new antibiotics, but also in a better understanding of autoimmune illnesses and therapy options. In addition IVIgs are used off-label for numerous illnesses and syndromes, some of which would merit further scrutiny. An EMEA Expert Meeting was recommended to address these issues that have already been highlighted in a circulated Committee for Medicinal Products for Human Use (CHMP) Concept Paper (EMEA/CHMP/BPWG/151426/2004, March 2005)[1]. This Concept Paper received numerous comments from the interested parties. The Expert meeting was planned to discuss the question of whether the currently recommended studies, "established indications" and their respective posologies require modification to more adequately reflect current clinical practice with IVIgs.

Furthermore, IVIgs used in other areas have proved beneficial and the possible inclusion of new indications may reflect current clinical practice. In the case of rare indications, there is the question of the extent of clinical data needed before the indication can be considered as "established" for IVIgs. Since there is a need for IVIg treatment of children, more specific guidance relating to the clinical investigation of IVIg products in paediatric populations needs to be considered, taking into account the Regulation on Medicinal Products for Paediatric Use[2,3]. The outcome of the Expert Meeting will provide the basis for Blood Product Working Party's (BPWP) revision of the guidance on the clinical investigation of IVIg and on its core SPC. It is intended that this general guidance will be complementary to specific advice provided for individual products through scientific advice or protocol assistance and the work of the Paediatric Committee. The Expert Meeting agenda and list of participants are provided in Annex II and III of this report.

OPEN SESSION ON 5 – 6 JULY 2006

DAY 1, SESSION 1 INTRODUCTION TO THE TOPIC

1) Introduction – M. Haase (Chairman of BPWP, CHMP member)

In his introduction, M. Haase outlined that the aims of the workshop were to discuss the revision of the “established indications”, to consider new indications and the specific concerns of the paediatric population. These considerations should be based on the current guidance of the CHMP for IVIg products (i.e. the core SPC and the Guidance on Clinical Investigations) and the European Pharmacopoeia (Ph. Eur.) Monograph 0918.

2) Regulatory framework - G. Silvester (EMEA Secretariat)

<u>Current EU legislation and its relevance for IVIgs</u>

The routes of a Marketing Authorisation Application (MAA) encompass the centralised procedure (CP), the mutual recognition procedure (MRP)/decentralised procedure and the national procedure.

The CP is optional in cases of significant innovation or in the interest of patients in the EU; it is however mandatory for orphan medicinal products (definition: for life threatening or chronically debilitating conditions with an incidence of not more than 5:10,000 persons in the European Community) or biotechnologically developed medicines. Orphan Medicine status is accompanied by incentives (e.g. market exclusivity for 10 years).

In addition, a market exclusivity of 1 year is possible for a new indication for a well-established substance, provided that significant pre-clinical or clinical studies were carried out in relation to the new indication.

The regulatory mechanisms for authorisation of products with limited data are authorisation under “exceptional circumstances” (e.g. if the indication is very rare) and “conditional authorisation”, which allows for earlier MAA of products intended for chronically or seriously debilitating /life-threatening diseases where it is considered that the product is of public health interest including whether it fulfils an unmet medical need. In both cases, specific post-authorisation commitments are required.

A further regulatory tool is the EU Risk Management Plan (RMP) which consists of 2 parts (Part I contains a Safety Specification and a Pharmacovigilance Plan and Part II a Risk Minimisation Evaluation and, where needed, a Risk Minimisation Plan). An EU RMP is to be submitted with an MAA for a new active substance or biosimilar substance, for a generic/hybrid medicinal product where safety concerns have been identified with the reference medicinal product, and where a significant change in a marketing authorisation has occurred.

3) IVIg guideline – relevance of the ITP model - J. Kerr (Paul-Ehrlich-Institut)

Idiopathic thrombocytopenic purpura (ITP), an auto-immune illness with low platelets (< 20,000/µl), lends itself as a model for IVIg’s immunomodulatory function as:

- it is conveyed by known antibodies (anti GPIIb/IIIa or/and Ib/Ix)
- it can be studied in adults and children of both sexes
- the surrogate marker (platelets) levels are easily measured and correspond to clinical manifestations in form of mucocutaneous bleeding
- the response to IVIg occurs within 5 days
- the response can be compared with other treatments (e.g. cortisone) or other IVIgs

- certain functional aspects of IVIgs are thought to be relevant in ITP (Fc-function, interaction with dendritic cells, anti-idiotypic antibodies). IVIgs with impaired/modified Fc-region do not offer the same platelet response as non-modified IVIgs.

3a) IVIg guideline – regulatory perspective - G. Silvester (EMEA Secretariat)

A MAA for an IVIg product requires a full dossier. An application based on biosimilarity to another IVIg product is possible but not recommended. The current approach for data requirements is described in the IVIg guideline. Data on quality, biological characteristics and pharmacokinetics (PK) should indicate that the product shows the typical properties of an IVIg. If PK, efficacy and safety are sufficiently shown in primary immunodeficiency (PID) and ITP, then the remaining "established" indications (Guillain Barré Syndrome (GBS), allogeneic bone marrow transplantation (ABMT) and Kawasaki disease) will be granted without further trials. The scientific rationale for this approach is that, on the basis of the required data package, efficacy in the other "established" indications can be expected.

4) Licensing IVIgs in US in non-PID indications: ITP Trial Requirements - L. R. Pierce (FDA, CBER)

As yet there is no FDA guidance document for ITP. Efficacy would be easier to demonstrate in chronic (> 6 months) than in acute ITP. A typical design would thus encompass chronic non-pre-medicated ITP patients (children or adults) with platelets < 20,000/µl. The primary endpoint would be the percentage of patients with platelets of > 50,000/µl by day 5-7 and the secondary point the durability of response. In the US, licensed products show response rates of > 79%. Safety investigation should cover adverse events related to the infusion and to the infusion rate and percentage of patients and/or infusions with adverse events.

In the US, ITP is not used as a model for the response to IVIg in other diseases. Each disorder must be studied separately as there is not considered to be a compelling scientific basis for extrapolation.

IVIg products differ in their specific antibody content and activities and in their safety profiles (e.g. due to different excipients, IgA content etc). One head–to-head efficacy study comparing 2 IVIg products reported significantly fewer sino-pulmonary infections with one of the products. The data are insufficient to satisfactorily answer the question whether there are efficacy differences between the various IVIg products.

5) Statistical Considerations, Guideline on Small Populations - P. Volkers (Statistician, Paul-Ehrlich-Institut)

The hierarchy of the level of evidence is as follows:

1) Meta-analyses of (good quality) randomised controlled trials
2) Individual randomised controlled trial
3) Meta-analyses of observational studies
4) Individual observational study
5) Published case reports
6) Anecdotal case reports
7) Expert opinion

Reference was made to the CHMP Guideline on clinical trials in small populations[4]. The same standards as for other products apply in MAA in small populations (e.g. choice of endpoints, of controls, blinding). Apart from being a source for historical, external control, patient registries may be used as a source of information for planning randomised studies.

Different designs may make better use of few available patients (sequential, adaptive, n-of-I-trials, response adaptive trials). Adding prognostic factors may increase the efficiency of analysis and including prior assumptions should be pre-planned and validated.

6) European Paediatric Initiatives (Roles of the Paediatric Committee/ SAWP/CHMP) - N. Seigneuret (EMEA Secretariat)

The main principles of the draft European Regulation[a] are to promote the development of medicines to be used in children, to increase information, and to develop ethical high quality clinical research in children. The Regulation includes the creation of a Paediatric Committee at the EMEA, and a system of rewards and obligations on companies developing medicinal products irrespective of whether they are for use in children or adults.

Companies must agree the paediatric development of new medicines with the Paediatric Committee ahead of the submission for marketing authorisation or, for patented products already authorised, ahead of the submission of an application for a new indication, a new pharmaceutical form or a new route of administration. The reward for agreeing and completing the paediatric development is a 6-month extension of the patent (i.e. of the Supplementary Protection Certificate). There will be development waivers for medicines intended for use in disorders that do not occur in childhood. There will be also the possibility of deferrals of the initiation and/or completion of paediatric trials with respect to adult trials.

Other measures in the Regulation include the development of an EU paediatric research network and a database of clinical trials performed in children with public access, in order to avoid duplication of trials. Public funding would be provided for the development of old products, probably through the European Framework programmes.

7) Discussion Day 1/Session 1

7.1 Should IVIg be assessed as a group or as individual products?

IVIgs show differences concerning excipients (e.g. sucrose, maltose), IgA levels and antibody titres. In addition the guidance on IVIgs make it clear that they are individual medicinal products and not generics. Nevertheless, the clinical experts felt from their extensive experience that the various products were interchangeable as far as efficacy was concerned. The production standards especially for viral safety are increasing continuously and being implemented for each IVIg. Well defined quality specifications and a thorough biological characterisation of the IVIg product make an important contribution to establishing whether the product has the typical properties of IVIg and thus ensuring high quality products. The core SPC enables standard wording for all products. However, there are too few published data on head-to-head comparisons of IVIgs to confirm or reject the clinical experience of interchangeability. Thus, a definitive statement remains difficult. Currently, the main differences in the clinical setting are seen in the realm of side effects due to excipients and IgA levels.

If a product were to be manufactured by a novel manufacturing process, particular efforts should be made to show that it retains the typical properties of an IVIg.

The participants seemed to be in favour of maintaining the general approach of the CHMP Guideline:

- quality, biological characteristics and pharmacokinetics should indicate that the product shows typical properties of an IVIg,

- clinical efficacy should be demonstrated in PID and ITP, then other "established" indications can be claimed without clinical data in these indications with the specific product.

[a] The regulations on medicinal products for paediatric use were finalised and published in December 2006[2,3].

7.2 IVIgs used in other areas have proved beneficial and the possible inclusion of other indications may reflect current clinical practice. What data requirements are needed for each new indication?

In the case of rare indications, there is the question of the extent of clinical data needed before the indication can be considered as "established" for IVIgs. This includes consideration of statistics for small populations.

The Guideline on Small Population (CHMP/EWP/83561/2005)[4] is of limited help, as precise numbers of patients, infusions, trial requirements and stopping rules are not specified. However, meta-analyses of randomised controlled trials as provided by Cochrane reviews rank in position I of the level of evidence. In general, the study design and approach should be the same as in studies with large populations. Controls and success criteria should be well-defined, if a randomised controlled study is not possible. Epidemiological data and data from patient registries may help in assessing efficacy and safety

7.3 Idiopathic (autoimmune) thrombocytopenic purpura (ITP):

Is there a need to distinguish between modified and non-modified IVIg products in the criteria for proof of efficacy and safety in ITP? (Products that are Fc-modified have shown to be of limited efficacy in ITP.).

The statement in the introduction to the IVIg Guideline "For other immunoglobulin products (fragmented, chemically modified), the same criteria apply for proof of efficacy and safety" was considered inappropriate and should be deleted. The Guideline should indicate that it does not relate to fragmented and chemically modified products. Such products do not have the typical properties of IVIgs. In general they are no longer marketed, but this was no guarantee that the situation would not arise in the future.

R. Thorpe provided laboratory data supporting the clinical evidence that Fc modified IVIgs indeed behave differently and should not be treated the same in the immunomodulatory setting.

It was further discussed that ITP is a usable model for a host of immunomodulatory aspects, in particular an intact Fc function is needed, as otherwise the platelet enhancing effect is diminished. ITP provides a clinically relevant surrogate market (platelet increase) that is readily measured in both sexes and all age groups.

Other questions

It remained unclear as to how the regulation on medicinal products for paediatric use and the requirement for Paediatric Investigation Plans (PIP) would be adapted to IVIgs and where waivers would be possible due to the extensive existing data.

In the case of PIDs, children are routinely included in the trials; in the case of ITP, only adults were hitherto requested by the guideline.

In PK studies to date, no distinct differences have been seen between the adult and paediatric population in the clinical settings of IVIg administration or in the home settings of subcutaneous immunoglobulin administration.

DAY 1, SESSION 2 GENERAL ASPECTS

1) Mechanism of action of IVIg: where do we stand? S. Kaveri, (Centre de Recherche des Cordeliers, Paris)

Self-reactive antibodies (and T cells) do exist in physiological conditions (= natural auto-antibodies). The pattern of expression of a variety of auto-autoantibodies differs decidedly between healthy individuals and those with auto-immune illness. IVIgs contain antibodies to non-self, to self-antigens and to other antibodies (anti-idiotypes). Any or all of these antibodies may play a role in immunomodulation. The mechanisms of immunopathogenesis are complex and the potential mechanisms of action of IVIg are also complex. Potential mechanisms of action of IVIg in autoimmune and inflammatory diseases were illustrated. IVIg may intervene at various steps in auto-immune and inflammatory processes: possible mechanisms could include modulation of T-cell, B-cell and monocyte proliferation and activation; neutralisation of auto-antibodies by anti-idiotypic antibodies; shifting of balance of Th1 to Th2 cells with decrease in secretion of pro-inflammatory cytokines; blockade of Fc receptors on macrophages; priming of dendritic cell regulatory activity.

2) Indications of IVIg - L. Mouton (CEDIT IVIg-Group, Cochin Hospital)

CEDIT is a scientific board of specialists at Parisian hospitals working in the fields of internal medicine, transfusion medicine, paediatrics, neurology, intensive care, immunology, statistics and pharmacology. It convenes to examine IVIg indications, to provide rationale for recommendations and to initiate clinical trials. Since coming into existence it has been able to stabilize the amount of IVIg consumption in Paris compared to the growing consumption in the rest of France.

IVIg indications are divided into 3 categories:

Group I: recognised indications (authorised and/or scientifically validated)

Group II: (indications that are under evaluation)

Group III: (not recognised indications)

In Group I CEDIT also includes corticoresistant dermatomyositis (DM), myasthenia gravis (MG), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), multifocal motor neuropathy (MMN) with conduction blocks (and Stiff Person Syndrome) i.e. those indications that are under discussion at the EMEA IVIg Workshop. In Group III CEDIT does not see sufficient evidence for efficacy of IVIg in bone marrow allograft (except in patients with a primary immune deficiency), autologous stem cell transplantation, inclusion body myositis in the absence of oesophagus involvement or in multiple sclerosis.

3) Licensing of IVIg products for PID in the US - L. R. Pierce (FDA, CBER)

FDA is working on final guidance for trial design, the presentation was based on the current draft guidance. The current trial design calls for 40-50 PID patients receiving IVIg infusions every 3-4 weeks to be followed for 12 months thereby avoiding any seasonal bias. Serious bacterial infections (bacteraemia or sepsis, bacterial meningitis, osteomyelitis/septic arthritis, bacterial pneumonia, visceral abscess) should be statistically significantly less than 1.0 infection/subject/year. Diagnostic criteria for serious infections and the statistical evaluation were outlined.

Secondary endpoints (similar to those in the EU Guideline) are IgG trough levels, all other infections, antibiotic treatment, days lost from school/work, hospitalisations, fever episodes, and quality of life (QOL). Safety analysis encompasses all treatment emergent adverse events (TEAEs) with particular focus on temporal association to the IVIg infusion. Pre-medication is discouraged to avoid masking AEs. It is recommended to obtain PK data in 20 PID subjects and to analyse the relationship between total and specific pathogen IgG levels and serious/non-serious infections and their causative agent(s). The Pediatric Rule is to be adhered to taking into account the number of children for each age group.

4) Adult PID and IVIg – Established/Unestablished indications - M. Seppänen (University Central Hospital, Helsinki)

New subgroups of hypo-and agammaglobulinemias were described and a rewording of the core SPC indications was proposed. With regard to the dosing of PID, most infections can be controlled by trough levels of 5.5 – 6.5 g/l. However, when comparing trough levels and infection rates, an additional benefit can be seen in trough levels of 6 – 9 g/l and doses should be adjusted for individual patients for infection prophylaxis to maintain long-term pulmonary function.

For adult selective antibody deficiency (SAD) (with or without IgA deficiency or IgG subclass deficiency), IVIg could play a role in case of bronchioectasis, recurrent otitis media, failure of antibiotics due to hypersensitivity, structural lung or sinus damage.

Isolated IgG subclass deficiency or selective IgA deficiency can currently not be recommended to be added to the established indications, due to an absence of evidence at present.

For other forms of unspecified hypogammaglobulinemia, where a patient with recurrent invasive infections does not fulfil any other diagnostic criteria and displays reduced or absent vaccination responses, M. Seppänen's current practice is to treat 6-12 months, to cover seasonal variation, in order to see if IVIg is effective.

5) Chronic lymphocytic leukaemia (CLL) and Multiple Myeloma (MM) - H. Chapel (University of Oxford)

CLL patients are currently being diagnosed earlier in life than was previously the case. At these early stages Igs may be low and bacterial infections may reduce QOL and productivity. There is little data on prophylactic antibiotic use; in general, cotrimoxazole is recommended, if steroids have been given or neutropenia is prevalent. Antivirals are given if the patient is on chemotherapy and thus at high risk of opportunistic viral infection. Prophylactic IVIg may be administered if IgG < 4.0 g/l and if previous bacterial infections have occurred.

The risk factors for a major infection (viral, fungal and bacterial) in CLL are Binet grade C disease and previous chemotherapy. The British Committee for Standards in Haematology drew up guidelines recommending that CLL patients with hypogammaglobulinemia and recurrent bacterial infections, especially those *in whom prophylactic antibiotics have failed* should be treated with prophylactic IVIg (grade A recommendation, level 1b evidence). The question of the correct dose to prevent all bacterial infections is still unresolved.

MM, a malignancy of plasma cells, is an aggressive tumour that affects patients older than 40 years of age. The diagnosis is made when the patient becomes symptomatic; life expectancy is approx. 3-5 years. The risk of fungal and viral infections is high during and after chemotherapy and highest during the first 3 months after diagnosis. Bacterial infections are associated with low serum immunoglobulin levels. One randomised controlled trial with IVIg showed significant benefit for patients in plateau phase with recurrent infections. Since then therapy for MM has changed and now consists of autologous stem cell support, prophylactic antibiotics, antifungal and antiviral therapy - however there have been no new trials of infection prevention with IVIg.

Pneumococcal immunisation efforts showed suboptimal responses of 45-61%. IVIg was only beneficial in non-responders. Thus, the suggested SPC wording is: Plateau phase MM patients with hypogammaglobulinemia and recurrent bacterial infections *who have failed to respond to pneumococcal immunisation.*

5a) Clinical use of IVIg in CLL - M. Anderesi (Talecris/Bayer, PPTA)

CLL is the most common form of adult leukaemia in the western hemisphere accounting for 30% of the leukaemias in this population. Secondary hypoglobulinemia, occurring in 60% of CLL patients is the major immune defect leading to increased risk of infection. Studies have shown that IVIg administration leads to fewer bacterial infections and fewer days in hospital. The retrospective study of Hensel *et al.* is inconclusive due to methodological deficiencies (small number of patients treated with IVIg (10/187) and a heterogeneous patient population). Thus, the CLL indication should remain in the SPC as it is.

6) IVIg and allogeneic hematopoietic stem cell transplantation (HSCT) - A. Buzyn Lévy (Hôpital Necker-Enfants Malades, Paris)

The number of HSCT performed per year in France has been increasing over the last decades and was 982 in 2004; in the EU the number is approx. 8000/year. HSCT is indicated for haematological malignancies, certain congenital diseases (including PIDs) and solid tumours, aplastic anaemia, non-Hodgkin lymphoma and Hodgkin's disease. The number of related or unrelated donors in the international registry is approximately 10 million. In addition 300,000 samples of cord blood are banked. The main immune complications of HSCT are rejection, Graft-versus-Host disease (GvHD) (70%, main cause of mortality) and a secondary immunodeficiency lasting about 1 year after transplantation. IVIg has been employed in this setting from 1987-1993 during which 5 randomised non-placebo controlled studies demonstrated prophylactic effect of IVIg in acute GvHD, infections and mortality associated with cytomegalovirus (CMV) disease.

A more recent placebo-controlled, double-blind study by Cordonnier *et al.* assessed dose-effect of IVIg prophylaxis (placebo, 50, 250, 500 mg/kg) in allogeneic sibling stem cell transplantation. Patients with hypogammaglobulinemia < 4 g/l were excluded. Baseline characteristics were similar in the four groups; the rate of side effects was also similar in the first three groups, but more than doubled in the fourth dosing group. There was no benefit of IVIg over placebo (at any dose) in preventing infection (including CMV infection), interstitial pneumonia, chronic GvHD or treatment-related mortality. Although there was a dose effect of IVIg to prevent acute GvHD, this showed no benefit on overall survival. A significant dose effect of higher doses was seen in the increased incidence of severe grade III veno-occlusive disease (VOD).

Thus, IVIgs should not be used for prophylactic treatment in conventional myeloablative HSCT as there is no benefit on survival and the risk of VOD is increased. IVIg can be given in a prophylactic setting for secondary B-Cell deficiency (IgG < 4g/l) after HSCT. The role of IVIg in the new HSCT strategies remains yet to be determined.

6a) IVIg in Allogeneic Bone Marrow Transplantation (ABMT) - I. Andresen (ZLB Behring)

ABMT is accompanied by severe secondary immune deficiency rendering the patient susceptible to opportunistic infections, of which CMV is the most prominent. Other complications are acute and chronic GvHD.

Former studies demonstrated benefit of IVIg in ABMT recipients and thus the treatment of infections and GvHD after ABMT were included as indications. More recent studies (Cordonnier 2003) could not fully replicate the benefits previously shown.

The Centers for Disease Control (CDC) recommendations (2000) for IVIgs in ABMT are the following

- The prevention of bacterial infections in ABMT patients with severe hypogammaglobulinemia (IgG < 4 g/l) within the first 100 days after transplantation

- Second line treatment to prevent or modify the severity of GvHD in patients who do not tolerate the immunosuppressive regime
- The dose should be tailored to maintain serum IgG trough levels of > 4-5 g/l

Comment: These CDC recommendations pre-date the Cordonnier study.

7) Safety of IVIg for Human Use - B. Keller-Stanislawski (Paul-Ehrlich-Institut)

Safety issues can be divided into 2 categories

- Common and mild adverse drug reactions (ADRs) (headache, nausea, fever, arthralgia, myalgia)
- Rare and serious ADRs (anaphylaxis, aseptic meningitis, eczematous skin reaction, haemolytic anaemia, acute renal failure and thrombotic complications)

There are approximately 100 single case reports of acute renal failure (ARF). A renal biopsy typically shows swelling and vacuolisation of the epithelial cells of the glomeruli. Sucrose containing IVIg products are the main but not only (e.g. sorbitol) culprit. This possible ADR is addressed in the SPC. More information is needed on other carbohydrate excipients.

The risk factors for circulatory impairment and hence for thromboembolic events are also covered by the SPC. Circulatory impairment in conjunction with a rise in plasma viscosity (IVIg administration) may trigger a thromboembolic event.

IVIgs containing hemolysins can enhance red blood cell sequestration in patients who should therefore be monitored for several days post high dose infusions for symptoms of hemolysis. Once the diagnosis is confirmed the appropriate treatment should be initiated. This aspect could be taken into section 4.4 of the SPC.

Maltose containing products may interfere with blood and urine glucose measurements in certain assays and cases of hypoglycaemia have been reported due to false positive testing during therapy with the concerned IVIg. This interference of maltose in glucose assays should be incorporated in the SPC.

Encephalopathy and neurodegenerative disorders in relation to IVIgs have not been proven, but further information may become available through the ESID registry (European Society for Immunodeficiencies).

8) IVIg: PPTA Perspective - F. Fabbrizzi (Kedrion, PPTA)

Due to finer diagnostic tuning more patients are being diagnosed with PID and have no therapeutic alternative other than IVIg replacement therapy. In addition, IVIgs are being used in a wide range of on- and off-label uses, particularly in the field of immunomodulation, where IVIgs often have a more favourable risk/benefit profile compared with alternatives. Thus, the demand for IVIgs world-wide is growing.

Conventional paradigms of clinical development often do not apply to IVIgs due to small populations with rare disorders or administration of IVIgs when other therapies have failed or are unacceptable (e.g. pregnancy/post partum). Thus, individualised therapies, where the physician plays a key role in the decision making should be reflected in the core SPC.

9) How to keep industry motivated to document the proper use of IVIg? - T. Waegemans (LFB, IPFA)

In vitro testing has shown difference in biological activity of different IVIg batches. There is however currently no clinical evidence available to prove a difference in efficacy from one unmodified brand of IVIg to another

In some indications (e.g. for Myasthenia gravis (MG)) studies were performed with only one brand of IVIg thereby making any extrapolation difficult. Helpful advice for industry on how to gauge the need for studies comes from e.g. the CEDIT (Paris) especially Group II indications, from regulatory agencies, and the medical community.

Expected Marketing Authorisation requests in the near future will encompass: MG, CIDP, ANCA positive vasculitis, acquired von Willebrand disease.

A reward/incentive system is essential (e.g. EU/US orphan drug protection). In the US there is a patent extension in paediatric development; the EU is to follow suit with its paediatric investigation plan. IPFA proposes granting exclusivity (limited in time and territory) to a sponsor who has demonstrated efficacious use of IVIg in a given indication.

10) EU PID Draft Consensus Statement - D. Watters (International Patient Organisation for Primary Immunodeficiencies (IPOPI))

As a result of a collaboration of IPOPI, ESID, the International Nurses Group for Immunodeficiencies (INGID) and the European Federation for Immunological Societies (EFIS), an EU PID Consensus Statement[b] has been drawn up to cover the following main aspects:

PIDs are widely under-diagnosed, possibly as much as 95%. Thus, it is essential to implement standardized diagnostic criteria and tools, assess real prevalence and incidence and judge the impact of PID on public health. Educational campaigns are necessary to increase awareness and understanding of PID in the general public (e.g. differentiation between PID and AIDs) and healthcare professionals. Valuable information on PID will be retrieved from the future ESID registry.

11) Discussion Day 1, Session 2

11.1 Do the currently recommended studies, "established indications" and their respective posologies require modification to more adequately reflect current clinical practice with IVIgs?

Changes to the wording of the established indications and their posologies proposed during the meeting could encompass the following:

- Rewording of the PID indications
- CLL patients with hypogammaglobulinemia and recurrent bacterial infections *in whom prophylactic antibiotics have failed*
- plateau phase MM patients with hypogammaglobulinemia and recurrent bacterial infections *who have failed to respond to pneumococcal immunisation.*
- *prophylactic IVIg administration for secondary B-Cell deficiency (IgG<4g/l) after ABMT*

11.2 Primary immunodeficiency (PID) study requirements:

Is there scope for harmonisation of CHMP recommendations for pharmacokinetic, efficacy and safety studies in PID patients with FDA draft recommendations? (FDA draft guidance for comment purposes published in November 2005.)

By using the FDA classification of serious bacterial infections and other infections, clearer data on life threatening infections would emerge and thus enable a better comparison between products and also to historical controls. A 12 month study period would avoid a seasonal bias, which has caused some problems in past EU evaluations when only six month data were provided. The higher numbers of patients and the very detailed reporting of adverse events (AEs) required by the FDA guidance may contribute to questions such as whether PID patients suffer from different subsets/rates of AEs compared to other patients treated with IVIg.

[b] EU PID Consensus statement available at: http://www.eupidconference.com/Publications.aspx

The EU Paediatric Legislation would be very similar to that of the USA, thereby providing further scope for harmonisation. There is no robust data regarding the posology for paediatric PID. However, it was agreed that a loading dose of 800 mg/kg, followed by a starting dose of 0.4 g/kg per month given in 1 to 4 weeks, would be a pragmatic solution, if the clinical symptoms did not call for alterations. Data from registries might be helpful in the determination of the posology. Although lung function measurements were felt to be important (as pulmonary problems are seen in adolescent patients), it was not clear if this was correlated to IVIg dosage or if it would be measurable within a clinical trial.

11.3 Are the current dosage recommendations and targeted trough levels of IgG given in the cSPC still adequate for PID patients? Recent literature suggests higher doses should be used, if patients develop more than 2 severe infections/year despite standard therapy.

The dosing in PID should be tailored to the patients needs and higher doses have been shown to be successful in one study especially if severe infections increase. Thus, trough levels should be assessed in conjunction with the incidence of infection. To reduce the rate of infection, it may be necessary to increase the dosage and aim for higher trough levels (9 g/l).

11.4 Chronic lymphocytic leukaemia (CLL)

What is the current role of IVIg in CLL treatment in view of the wide spectrum of antibiotics that has been developed to combat infectious complications?

IVIg still has a therapeutic role in CLL, however, the indication should be modified to: CLL patients with hypogammaglobulinemia and recurrent bacterial infections *in whom prophylactic antibiotics have failed* should be treated with prophylactic IVIg.

The question of the correct dose to prevent all bacterial infections is still unresolved.

11.5 Allogeneic bone marrow transplantation (ABMT)

What is the current role of IVIg in ABMT treatment? In recent studies the use of prophylactic IVIg in ABMT has been questioned. In one recent study there was no benefit over placebo.

IVIgs should not be used for prophylactic treatment in conventional myeloablative HSCT as there is no benefit on survival and the risk of VOD is increased. IVIg can be given in a prophylactic setting for secondary B-Cell deficiency (IgG<4g/l) after HSCT; this may be added as a further secondary indication along with CLL and MM. Other indications (GvHD, viral complications) show no overall benefit when treated with IVIg. The role of IVIg in the new HSCT strategies remains yet to be determined.

11.6 General review of contraindications, precautions and warnings, and undesirable effects taking into account the revision of the SPC Guideline.

Most main ADRs are currently covered by the core SPC. Some rewordings should however be considered:

- Hemolysins can enhance red blood cell sequestration. Patients should therefore be monitored for several days post high dose infusions for symptoms of hemolysis. Once the diagnosis is confirmed the appropriate treatment should be initiated.

- The interference of maltose in glucose assays (false positive testing) and resulting cases of hypoglycaemia should be incorporated as a product specific warning in the Core SPC.

- Section 4.8 of the Core SPC would be updated in line with the SPC guideline.

DAY 2, SESSION 1 NEUROLOGICAL ASPECTS

1) Introduction

The Chairperson of this session, R. Hughes, gave a brief introduction on inflammatory neuropathies and what was known on the causes of the diseases.

J. Kerr highlighted key aspects that needed to be considered including: the level of evidence currently available for indications that affected small populations; differences between trial designs (e.g. inclusion criteria, phase of disease, different scales for evaluation) making an overview difficult; whether IVIg is used alone or in combination with other treatments; whether there are data with more than one IVIg product; length of treatment and paediatric issues.

2) Treatment of Multifocal Motor neuropathy (MMN); evidence for IVIg treatment - I. van Schaik (University of Amsterdam)

In the 2005 Cochrane Review on MMN and IVIg therapy, 4 randomised controlled trials using different IVIgs met the previously defined review criteria. The data were reviewed by two independent reviewers and classified into various quality levels. The statistical analysis tested for heterogeneity and pooled dichotomous and continuous data resulting in relative risk estimates and weighted effect sizes, respectively. The 4 randomised, placebo-controlled trials dated from 1994-2001 and encompassed a total of 34 patients. Different disability scales were used making the pre-defined primary endpoint of change in disability difficult to assess. The test showed a trend for improvement under IVIg that however was not significant (p=0.08). For the secondary endpoint ‘increase in muscle strength’ the effect of IVIg was significant (p=0.0005). For resolution of at least one conduction block (secondary endpoint), IVIg also showed a trend for improvement (p=0.06) over placebo. For 2 trials, side-effects under IVIg were greater than placebo (however none were serious), for the 2 remaining trials, no side-effects were reported according to a personal communication of the investigators. Approximately one third of the patients had > 12 months remission, one half needed repeated IVIg infusions, and a quarter additional immunosuppressant treatment.

In another 94 case reports (487 MMN patients) that were reviewed, an improvement of muscle weakness was seen in 81% of patients and an improvement of disability was seen in 74%.

The 2006 European Federation of Neurological Societies (EFNS)/Peripheral Nerve Society (PNS) Guideline recommendation[5] is to use IVIg (in a total dose of 2 g/kg given over 2 to 5 days) as a first line treatment (level A), as corticosteroids are not recommended and toxicity makes cyclophosphamide a less desirable option. If the initial IVIg treatment is effective, repeated infusions should be considered (Level C). Furthermore, the frequency of maintenance therapy should be guided by the individual response, whereby typical treatment regimens are 1 g/kg every 2–4 weeks or 2 g/kg every 4–8 weeks. On the other hand if IVIg is not or not sufficiently effective then immunosuppressive treatment may be considered. However, for other immunosuppressive treatment no randomised controlled trials have been performed. Only retrospective and prospective case studies were available with beneficial effects mainly reported for cyclophosphamide. No effects were seen for corticosteroids and plasma exchange.

3) IVIg and chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) - I. van Schaik (University of Amsterdam)

In the 2002 Cochrane Review on CIDP and IVIg therapy, 6 randomised controlled trials* using different IVIgs met the previously defined review criteria. Four of these tested IVIg against placebo, one against plasma exchange and one against corticosteroids. The data were reviewed by two independent reviewers and classified into various quality levels. The statistical analysis was the same as for MMN. The review was updated in 2006, but no new studies were found.

The 6 randomised controlled trials dated from 1993-2001 and encompassed a total of 170 adult patients. As with MMN, different disability scales were used thereby encumbering the assessment. Other methodological issues were raised. In 3 studies the time point of assessing the primary endpoint was too early. Other concerns related to the definition criteria for CIDP.

IVIg was shown to be superior to placebo with a relative risk of 3.12 (1.72-5.67). Four different brands of IVIg were used. In one other trial, plasma exchange and IVIg were not significantly different in their short-term effects. In one further trial there was no significant difference in short-term effects of prednisolone from IVIg. Here the concern related to the regimen of prednisolone, the power of the study and the fact that it was prematurely stopped.

*

Vermeulen	1993	Central Laboratory of Bloodtransfusion service Amsterdam (currently Sanquin)
Dyck	1994	Gamimune, Miles Biological Products
Thompson	1996	Sandoglobulin
Hahn	1996	IVIg (Cutter Biological Products, Miles Inc; 5% human protein in 9-11% mannose)
Mendell	2001	Aventis Behring LLC (King of Prussia, PA) (formerly Centeon LLC) supplied the immunoglobulin (Pasteurized Gammart IV)
Hughes	2001	Sandoglobulin

3a) Clinical use of IVIg in CIDP - E. Rentz (Biotest; PPTA)

A guideline on the management of CIDP was drawn up by the EFNS/PNS and published in 2005[6]. The Task Force agreed on good practice points to define clinical and electrophysiological diagnostic criteria for CIDP and made the following recommendations:

(1) IVIg or corticosteroids should be considered in sensory and motor CIDP (level B recommendation)

(2) IVIg should be considered as the initial treatment in pure motor CIDP (good practice point)

(3) If IVIg and corticosteroids are ineffective, plasma exchange should be considered (level A recommendation)

(4) If the response is inadequate or the maintenance doses of the initial treatment are high, combination treatments or adding an immunosuppressant or immunomodulatory drug should be considered (good practice point)

(5) Symptomatic treatment and multidisciplinary management should be considered (good practice point).

4) IVIg for Myasthenia gravis (MG) - P. Gajdos (Hôpital Raymond Poincaré)

In the treatment of this autoimmune neuromuscular transmission disorder, one has to distinguish between severe stable MG and exacerbations or crises of MG. The treatment options for severe stable MG are anticholinesterase drugs, thymectomy, steroids, immunosuppressants and questionably plasma exchange. For exacerbations of MG, they are also anticholinesterase drugs, intensive care with mechanical ventilation, steroids and plasma exchange.

Severe-stable MG

Two randomised controlled trials for severe but stable MG were not adequately powered and there is no evidence from randomised controlled trials to determine whether IVIg for moderate or severe stable myasthenia gravis improves functional outcome or has a sparing effect on steroid dosage.

Exacerbations

In the 80s and early 90s, 7 open studies were performed including ≥ 10 patients and showing an overall beneficial effect of IVIg. A retrospective comparative study of 54 episodes of myasthenic crisis showed a better outcome with plasma exchange than IVIg but with a higher complication rate. Two case series supported a sparing effect of IVIg on steroid dosage. For IVIg and MG exacerbation, 3 randomised controlled trials have been performed of which 2 were adequately powered. The scales used were the Myasthenic Muscle Score (0-100) and the Quantified Myasthenia Gravis Score (0-39). One randomised controlled trial of IVIg versus plasma exchange showed similar responses but lower complication rates with IVIg. Thus, IVIg may be an option for treating exacerbation of myasthenia gravis. One randomised controlled trial did not demonstrate the expected superiority of IVIg 2 g/kg over IVIg 1 g/kg. For the treatment of MG exacerbation, 1 g/kg IVIg on a single day may be a sufficient dose. The same IVIg brand was used in these two studies.

5) IVIg in Myasthenia Gravis - R. Ricciardi (Hospital of Pisa)

R. Ricciardi is personally afflicted by the disorder and is President of the Italian Myasthenia Association (Associazione Italiana MIA Onlus), Specialist in Neurology and Head of Myasthenia Gravis Treatment Centre of the Hospital of Pisa.

In a 4-arm study in 90 patients classified according to Osserman, IVIg was added on to pyridostigmine bromide and prednisone (and azathioprine or cyclosporine A) and evaluated prior and 5 days after IVIg administration. After the combination treatment, the mean scores were improved for ocular, generalised and bulbar functions. The best results were in the treatment of myasthenic crisis and as a means to reduce the dosage of corticosteroids.

6) IVIg in autoimmune inflammatory myopathies, especially in dermatomyositis (DM) - D. Pongratz (Ludwig Maximillians University, Munich)

(presented by R. Hughes, apologies received from D. Pongratz)

Autoimmune myositis can be subdivided into 4 main types: dermatomyositis (DM), polymyositis (PM), sporadic inclusion body myositis (s-IBM) and myositis with extramuscular involvement. The clinical features, age and acuteness of onset, distribution of paresis, atrophy, myalgia, and also treatment options vary between these different types. The standard of care for DM/PM is steroids and immunosuppressants, but no randomised trials have been performed. To induce remission in severe DM and in PM with anti-signal recognition particle (anti SRP) - auto-antibodies, additional therapy with IVIg is administered.

DM is a complement-mediated microangiopathy affecting skin and muscle resulting in skin abnormalities, including subcutaneous calcifications, muscle weakness and disability. DM has a prevalence of 6/100,000 affecting females twice as often as males. In a randomised trial in 15 DM patients, the clinical muscle scores improved significantly more in 8 IVIg participants, than in 7 placebo participants (Dalakas 1993).

In s-IBM, a T-cell mediated inflammatory myopathy, unresponsive to corticosteroids and immunosuppressive drugs, some evidence suggests that IVIg may have a slight, but short-lasting, beneficial effect in a small number of cases. In a recent cross-over study (Walter *et al.*) in 22 patients, 90% were stabilized under IVIg and improvement was seen in a subjective rating scale.

7) Discussion Day 2/Session 1

7.1 Based on a review of current evidence, is there sufficient data to consider the following indications "established" for IVIgs? If not, what additional data would be needed?

MMN

CIDP

Second line therapy option:

Severe myasthenia gravis

Dermatomyositis

Multifocal motor neuropathy (MMN)

The currently available study results (4 randomised controlled trials, 4 different IVIg products) and meta-analyses consistently show an advantage for IVIg treatment for all parameters, for the secondary endpoint 'increase in muscle strength' the effect of IVIg was significant (p=0.0005). R. Hughes commented that disability scales are not designed for the upper limb disabilities seen in MMN and this could be the reason for the failure to show a significant benefit for disability. Thus the experts present considered that there is sufficient evidence for MMN as a first line indication for IVIg treatment.

The initial dosing suggestion is 2 g/kg given over 2-5 days for the first course. There is inadequate evidence to say whether patients who do not respond to a first course will respond to a second or third. To avoid missing a treatment responsive patient, it may be appropriate to try a second or even third course (e.g. two further courses of 1 g/kg at 4 weekly intervals). As there are no controlled data for long-term treatment, IVIg should be stopped if no improvement is seen after 3 months. If a patient responds to IVIg, attempts should be made at intervals to reduce the dose to discover whether the patient still needs IVIg and what dose is needed. The interval at which the titration is made varies but is usually not less than every 3 months or more than every 12 months. It may be preferable to have the patients treated at specialized centres.

Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)

Six randomised controlled trials were analysed in the Cochrane Review (2002 and 2006), four of these tested IVIg against placebo, one against plasma exchange and one against corticosteroids. The 4 randomised, controlled trials provide evidence that IVIg improves disability for at least two to six weeks compared with placebo. CIDP also responds to corticosteroids and plasma exchange. Thus, the experts present considered that there is sufficient evidence to regard IVIg treatment as a first line option for CIDP; the dosing suggestion is 2 g/kg given over 2 or 5 days for the first course. A similar approach to that described above for MMN may be followed to investigate the response to second or third courses of IVIg, and to check whether IVIg is needed long-term. IVIg shows similar efficacy to plasma exchange and oral prednisolone with less logistic effort than plasma exchange and possibly a better adverse event profile than corticosteroids. It may be preferable to have the patients treated at specialized centres.

Myasthenia gravis

Severe, but stable MG

Two randomised controlled trials for severe but stable MG were not adequately powered and there is no evidence from randomised controlled trials to determine whether IVIg for moderate or severe stable MG improves functional outcome or has a sparing effect on steroid dosage. Thus, P. Gajdos and R. Hughes considered that the data were insufficient for severe but stable myasthenia gravis, whereas R. Ricciardi argued for a broader use of IVIg based on her extensive experience.

MG exacerbations/crisis

The experts present considered that there was evidence for first line IVIg treatment in myasthenia gravis exacerbations based on the trials versus plasma exchange, as IVIg showed the same efficacy and better tolerability than plasma exchange.

Dermatomyositis and other autoimmune inflammatory myopathies

The trial of IVIg in dermatomyositis by Dalakas indicated a positive effect of IVIg but the numbers were very small (8 IVIg vs. 7 placebo). As second line treatment in corticosteroid-resistant DM, experience is that IVIg induces a 60-70% response rate. In juvenile DM, the long-term effects of corticosteroids should be avoided, possibly allowing for a first line therapy in this age group. For polymyositis the data are inadequate.

I. van Schaik argued that sporadic inclusion body myositis (s-IBM) should not be considered an inflammatory myopathy. However, regardless of the categorization, the experts present considered that the evidence of benefit is not substantiated. These patients currently have no other therapy option.

7.2 Recent literature recommends 2 g/kg dose for Guillain-Barré syndrome given over 2-5 days (Hughes, et al. Intravenous Immunoglobulin for Guillain-Barré syndrome. The Cochrane Database of Systematic Reviews, 2004: Issue 1 CE002063).

The current dose and the one used in the trials is 0.4 g/kg daily for 5 days in GBS.

DAY 2, SESSION 2 PAEDIATRIC ASPECTS

1) Use of IVIg in paediatrics - P. Rossi (Tor Vergata University, Rome)

P. Rossi highlighted the use of IVIg for children with HIV and recurrent infections and Kawasaki disease. It was concluded that the present posology for IVIg is still adequate for these conditions. He considered that the indication for children with congenital AIDS should be modified to include adolescents and to specify that it is for use in patients with recurrent bacterial infections.

2) Neonatal sepsis - R. Cooke (Liverpool Women's Hospital)

R. Cooke presented data for the use of IVIg in neonatal sepsis. At this point the data do not support the inclusion of treatment and prophylaxis of neonatal sepsis in the indication for IVIg. However, new data is expected for evaluation in the near future when the results of a large-scale multi-centre trial are available. He considered that there was no convincing evidence for efficacy of prophylactic IVIg in improving outcomes in preterm or low birth weight newborns.

3) Guillain Barré Syndrome in children and IVIg treatment - A. Nascimento (Hospital Sant Joan de Deu, Barcelona)

A. Nascimento presented data from the treatment regimen used for GBS in Spain.

4) Panel Discussion Day 2, Session 2

Points to be addressed:

4.1 Do the currently recommended studies, "established indications" and their respective posologies require modification to more adequately reflect current clinical practice with IVIgs in paediatric patients?

4.2 For each IVIg product, should additional data be requested in paediatric patients in indications already established?

4.3 Paediatric AIDS:

Should the indication be modified to define more precisely the current use of IVIg in paediatric AIDS?

4.4 Recent literature recommends a single 2 g/kg dose for Kawasaki's syndrome rather than two or more doses over 2-5 days.

4.5 Based on a review of current evidence, is there sufficient data to consider the following indications "established" for IVIgs? If not, what additional data would be needed?

- *Neonatal sepsis*
- *Prophylactic use IVIg in preterms.*

4.6 Based on a review of current evidence, what conclusions can be reached on IVIg use in paediatric neurological syndromes?

4.7 General discussion on paediatric trial design as part of small populations approach.

Some of these points had already been discussed in earlier sessions and were not addressed again during the panel discussion.

The experts felt that in general, no new efficacy data is required for the paediatric use of IVIg for the "established" indications. However, there may be a need for more data for adverse event and posology issues. For replacement therapy in PID, it was emphasised that IgG trough levels should be assessed in conjunction with the incidence of infection when deciding on posology for the individual patient.

The experts agreed that further data were needed to provide evidence of whether or not IVIg is beneficial in neonatal sepsis and prophylactic use of IVIg in preterm or low birth weight newborns.

The experts concluded that in the use of IVIg for paediatric CIPD, MG and GBS, extrapolation from the adult data was appropriate and further clinical trials in the paediatric population were not essential. Nevertheless, it is valuable to collect available data.

Even though the randomised controlled trial as a method for clinical trial was acknowledged to provide reliable data, other approaches were also recommended to be taken into account when generating data for the very rare conditions, including databases and patient registries, and post-authorisation studies. The emphasis should be on useful studies to complement current knowledge.

The open meeting concluded with a summary of the two days from the BPWP Rapporteurs, J. Kerr, C. Ratignier and P. Laitinen-Parkkonen. M. Haase, BPWP Chairperson, closed the meeting thanking all participants for their contributions.

RESTRICTED SESSION 7 JULY 2006 AND FOLLOW-UP DISCUSSIONS

In the Restricted Session the entire meeting was reviewed, the main aspects were discussed and are captured in the meeting report. The outcome of the meeting will provide the basis for BPWP's revision of the core SPC and Guideline for IVIg. The meeting had identified areas where IVIg is being used with promising results. Where indications are not taken into the core SPC as "established indications", applicants would need to submit sufficient data to support a MAA, making use of the available regulatory tools.

Additional information that warranted further attention regarding the revision of the core SPC and Guideline is reported in this summary.

Ph. Eur. Monograph and Biological data requirements

Knowledge of the manufacturing process and a very thorough biological characterisation of an IVIg product make an important contribution to establishing whether a product has the typical properties of IVIg. It was decided to review Section 2.1.1 of the Guideline, which covers biological data requirements, and update it as appropriate. The latest Ph. Eur. Monograph for IVIg would be taken into account as part of this review.

ITP Model

In the margins of the open meeting, there had been some discussion about whether a further clinical model was maybe needed to cover additional immunomodulatory properties of IVIgs. In follow-up discussions with experts after the meeting, it was felt that a further clinical model would prove extremely problematical to implement owing to the rarity and natural fluctuations of the neuroimmunological disorders in question. Finding an adequate pre-clinical model may be fraught with similar difficulties, in addition to its questionable applicability in the various human settings.

Regulatory aspects of rare indications and IVIg

For rare diseases, there is the possibility of a marketing authorisation under "exceptional circumstances" which calls for only a limited data set but also a commitment to fulfil specific obligations (e.g. clinical study and monitoring of treatment courses). The question arose whether this procedural tool could be used for an already authorised IVIg when a new rare indication is introduced by a variation.

The advice given by the EMEA was that "exceptional circumstances" could not apply in this case.

An alternative would be to submit a self-standing application for the new indication; this would allow the grant of a separate authorisation under exceptional circumstances. The MA cannot be granted under the same name as the existing authorisation. However, the company may link the names of both authorisations (e.g. by using qualifiers). (An exception to this requirement for a different name is the Paediatric Use Marketing Authorisation (PUMA) where the existing name can be kept.)

New information available after the expert meeting

Annex I of this report includes new information published after the expert meeting. Information from these publications is summarised without critical analysis. These publications will be taken into account in the revision of the CHMP guidance on IVIg.

REFERENCES

[1] Concept Paper on revision of: Note for Guidance on the Clinical Investigation of Human Normal Immunoglobulin for Intravenous Administration (IVIg) (CPMP/BPWG/388/95 rev.1)
Core SPC for Human Normal Immunoglobulin for Intravenous Administration (IVIg), (CPMP/BPWG/859/95 rev. 2) (EMEA/CHMP/BPWG/151426/2004, March 2005)
http://www.emea.europa.eu/pdfs/human/bpwg/15142604en.pdf.

[2] Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004. OJ L 378, 27.12.2006, pp. 1-18.

[3] Regulation (EC) No 1902/2006 of the European Parliament and of the Council of 20 December 2006 amending Regulation 1901/2006 on medicinal products for paediatric use. OJ L 378, 27.12.2006, pp. 20-21.

[4] Guideline on clinical trials in small populations (CHMP/EWP/83561/2005, 27 July 2006).
http://www.emea.europa.eu/pdfs/human/ewp/8356105en.pdf

[5] Joint Task Force of the EFNS and the PNS (Hughes RAC, Bouche P, Cornblath DR et al.). European Federation of Neurological Societies/Peripheral Nerve Society Guideline on management of multifocal motor neuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. Journal of the Peripheral Nervous System 11:1–8 (2006).
http://pns.ucsd.edu/Guidelines_multifocal_neuropathy.pdf

[6] Joint Task Force of the EFNS and the PNS (Hughes RAC, Bouche P, Cornblath DR *et al.*) European Federation of Neurological Societies/Peripheral Nerve Society guideline on management of chronic inflammatory demyelinating polyradiculoneuropathy. Report of a joint task force of the European Federation of Neurological Societies and the Peripheral Nerve Society. Journal of the Peripheral Nervous System 10: 220-228 (2005).
http://pns.ucsd.edu/Guidelines_CIDP.pdf

ANNEX I

Additional literature data published after the expert meeting

Additional data gathered from the literature after the meeting, is summarised here to complete information provided on the rare indications and will be taken into account during the revision process.

New information on multifocal motor neuropathy (MMN)

In MMN, 2 studies have shown progressive motor deterioration in most patients, correlated with electrophysiological signs indicative of axonal degeneration, while a third study (Cros *et al*, Rev Neurol (Paris). 2006 Jun; 162 Spec No 1:3S46-3S50) found signs of sustained clinical and electrophysiological improvement after a mean follow up of 7.25 years. The authors felt this to be due to the higher dosing in their study: 2 g IVIg/kg over a period of 5 days every 4 weeks for 3 months. Maintenance therapy was administered every 4 weeks with dose adjustment to prevent muscular strength deterioration.

In a recent retrospective study (Rev Neurol (Paris). 2007 Jan;163(1):82-8, Delmont *et al.*) covering 4 years in 17 patients, one third of MMN with conduction blocks patients had clinical improvement and required no further treatment, one third were IVIg dependent and one third never responded to IVIg. Electrophysiological data were comparable between the first and the last examination. No predictive factor was found for long-term response to IVIg.

In another review by Delmont et al (Neurology. 2006 Aug 22;67(4):592-6) in 37 patients and a median follow-up time of 7 years, patients with and without conduction block showed similar clinical features and a similar response to IVIg treatment.

New Information on myasthenia gravis (MG)

In a recent article “Guidelines for the treatment of autoimmune neuromuscular transmission disorders” by G. O. Skeie, S. Apostolski, A. Evoli, N. E. Gilhus, I. K. Hart, L. Harms, D. Hilton-Jones, A. Melms, J. Verschuuren, H. W. Horge published in the European Journal of Neurology 13 (7), 691–699 July 2006, guidelines were laid down based on references retrieved from MEDLINE, EMBASE and the Cochrane Library. Among the proposed practical treatment guidelines agreed upon by the Task Force, the following conclusion relevant to IVIg and MG was reached: IVIg and plasma exchange are equally effective for the treatment of MG exacerbations (level A Recommendation).

In a further article “IV immunoglobulin in patients with myasthenia gravis” by Lorne Zinman, MD, MSc; Eduardo Ng, MD; and Vera Bril, MD (NEUROLOGY 2007; 68:837–841), the effectiveness of IVIg in the treatment of patients with MG and worsening weakness was to be determined in a randomised, placebo-controlled, masked study. Methods: Fifty-one patients with worsening weakness due to MG were randomised to infusion with 2 g/kg of IVIg or an equivalent volume of IV dextrose 5% in water. The Quantitative Myasthenia Gravis (QMG) Score for Disease Severity, a validated clinical composite scale, was calculated by a masked observer at baseline and days 14 and 28. Results: In IVIg-treated patients, a clinically meaningful improvement in QMG Score for Disease Severity was observed at day 14 and persisted at day 28. The greatest improvement occurred in patients with more severe disease as defined by a QMG Score for Disease Severity greater than 10.5. The conclusion reached by the authors was that this study provided evidence for the effectiveness of IVIg in patients with worsening weakness due to MG.

New information on dermatomyositis (DM)

In an article by Dalakas (Int Immunopharmacol. 2006 Apr;6(4):550-6. Epub 2005 Dec 20) “The role of high-dose immune globulin intravenous in the treatment of dermatomyositis” the following conclusions were drawn: A double-blind placebo-controlled study demonstrated that IVIg is very effective in improving both the muscle strength and the skin rash. The clinical benefit, which was impressive in patients with early disease, was associated with improvement in the muscle cytoarchitecture. Quantitative histological studies in repeated muscle biopsies showed a statistically significant increase in the size of muscle fibres and the number of capillaries with normalization of the capillary diameter. Resolution of the aberrant immunopathological parameters, including interception of complement activation products and down-regulation of T cells, ICAM-I, VCAM, TGF-beta and MHC-I molecules, was also noted. Further, a number of immunoregulatory and structural genes were modified in the patients' muscle biopsies after therapy. The article concluded that IVIg is an effective second-line therapy for patients with DM incompletely responding to steroids.

New information on Guillain-Barré Syndrome (GBS) in Children:

From the Cochrane Library Issue 3 2006 (Hughes, Raphael, Swan, van Doorn) 3 studies including a total of 75 participants suggested that in children IVIg significantly hastens recovery compared with supportive care.

The review article in TSMJ Volume 6: Cases (www.tcd.ie/tsmj/2005/6067CGBS.pdf) (Childhood Guillain-Barré Syndrome: Comparing Intravenous Immunoglobulin Treatment with Supportive Care, by Sarah McLean, Sheng F. Oon,) concluded that the data in children concurred with the data on GBS in adults, and that timely use of IVIg reduces mortality and morbidity in a paediatric setting. However, IVIg use made no difference in the incidence of long-term sequelae of GBS. Sample sizes were small. Larger studies are needed in order to fully explore the benefits of IVIg with regard to these outcome criteria. Logistically and ethically, this would be difficult and no randomised controlled trials have been done to date for this reason. Acute relapse was a new phenomenon, which had not been previously noted in the pre-IVIg era and warrants further investigation.

ICE Study: Intravenous immunoglobulin (10% Caprylate / Chromatography-purified IVIG, IGIV-C) in the treatment of CIDP

HP Hartung
ICE Study Group

Thieme-connect /Abstract, Akt Neurol 2007; 34, DOI: 10.1055/s-2007-987618.
(http://www.thieme-connect.com/ejournals/abstract/aktneu/doi/10.1055/s-2007-987618)

Objectives: The aim of the study was to examine the therapeutic efficacy of IVIg (IGIV-C 10%) compared to placebo in CIDP patients.

Background: IVIg is the preferred first line treatment of CIDP in many centres, as feasibility and handling is easier than the implementation of a plasma exchange. Based on a few smaller studies, IVIg is only authorized in a few countries for this indication. The ICE study is the largest study so far aiming to provide conclusive evidence for the effectiveness of IVIg in this disabling immunoneuropathy.

Design / Methods: This study is an international, multicentre, prospective, double-blind, placebo-controlled, parallel-designed study, with a cross-over for those patients who worsen under treatment. 117 patients with CIDP (de novo or pre-treated) were included, if the neurophysiological INCAT criteria were fulfilled and they had an INCAT disability score of 2-9. Initially, patients received 6 months verum or placebo, if they improved at least 1 point on the INCAT Disability Scale they could then proceed to be re- randomised to a blinded extension study. The primary endpoint was the disability after 6 months or the last INCAT Disability Score after the first infusion.

Results: The study was conducted in 31 centres in 10 countries worldwide. The analysis of the data so far, has shown a clear therapeutic effect of IGIV-C for CIDP.

Conclusion of the authors: In the largest study to date in CIDP, the efficacy of IVIg therapy has been shown.

ANNEX II

London, 4 July 2006
Doc. Ref: EMEA/CHMP/BPWP/307124/2005

PROGRAMME

EXPERT MEETING On Revision of Core SPC and Note for Guidance for human normal Immunoglobulin for intravenous administration

WEDNESDAY 5 JULY 2006 – THURSDAY 6 JULY 2006

1. Introduction

The current Note for Guidance (NfG) on the Clinical Investigation of Human Normal Immunoglobulin for Intravenous Administration (IVIg) (CPMP/BPWG/388/95 rev.1) and the Core SPC for Human Normal Immunoglobulin for Intravenous Administration (IVIg), (CPMP/BPWG/859/95 rev. 2) have been in operation since December 2000. Medical knowledge and treatment regimens in the areas covered by the NfG and cSPC are in a state of continual development. Especially the past 5-10 years have seen many changes e.g. in the therapy of AIDS, in the use of new antibiotics, but also in a better understanding of autoimmune illnesses and therapy options. In addition IVIgs are used off-label for numerous illnesses and syndromes, some of which would merit further scrutiny. An EMEA Expert Meeting was recommended to address these issues that have already been highlighted in a circulated Concept Paper drawn up by the Blood Products Working Party (BPWP). The circulated Concept Paper received numerous comments from the interested parties.

The Expert meeting is planned to discuss the question of whether the currently recommended studies, “established indications” and their respective posologies require modification to more adequately reflect current clinical practice with IVIgs.
Furthermore, IVIgs used in other areas have proved beneficial and the possible inclusion of other indications may reflect current clinical practice. In the case of rare indications, there is the question of the extent of clinical data needed before the indication can be considered as “established” for IVIgs.
Since there is a need for IVIg treatment of children, more specific guidance relating to the clinical investigation of IVIg products in paediatric populations needs to be considered, taking into account the Regulation on Medicinal Products for Paediatric Use, which is in development.

The outcome of the Expert Meeting will provide the basis for BPWP’s revision of the guidance on the clinical investigation of IVIg and on its core SPC. It is intended that this general guidance will be complementary to specific advice provided for individual products through scientific advice or protocol assistance and the work of the future Paediatric Committee. In addition, a report of the Expert Meeting will be published on the EMEA website.

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2. Expert Meeting

It is proposed to consider the following aspects:

A. Note for Guidance:

A: I. Reconsider the data necessary to support the safe and effective use of IVIg in the established indications.

PRIMARY IMMUNODEFICIENCY (PID) STUDY REQUIREMENTS

Review the FDA recommendations (draft guidance for comment purposes only published in November 2005) for pharmacokinetic, efficacy and safety studies in PID patients, in order to see if there is scope for harmonisation of recommendations.

- Idiopathic (autoimmune) thrombocytopenic purpura (ITP)

Review whether there is a need to distinguish between modified and non-modified IVIg products in the criteria for proof of efficacy and safety in ITP. (Products that are Fc-modified have shown to be of limited efficacy in ITP.)

A: II. Paediatric Use

The clinical studies needed to support regulatory approval for treatment of children.

- A systematic review of the literature to assess the benefit/risk of IVIg use in paediatric patients, discussing both currently established and new indications.
- Consideration of whether additional clinical data in paediatric patients are needed for currently established indications.
- For each new indication, general discussion on paediatric trial design as part of small populations approach.

A: III The data needed to support an indication in rare disorders.

B. Core SPC:

B: I. Changes to currently established indications:

- Chronic lymphocytic leukaemia (CLL)

What is the current role of IVIg in CLL treatment in view of the wide spectrum of antibiotics that has been developed to combat infectious complications? It is argued in a recent retrospective study (Hensel, Br J Haematol. 2003 Aug; 122(4):600-6) that disease activity and pre-treatment are the major risks for infectious complications in CLL.

- Allogeneic bone marrow transplantation (ABMT)

What is the current role of IVIg in ABMT treatment? In recent studies the use of prophylactic IVIg in ABMT has been questioned. In one study there was no benefit over placebo.

- Paediatric AIDS

Review whether the indication should be modified to define more precisely the current use of IVIg in paediatric AIDS.

B.II: New Indications to be discussed include:

1. Multifocal Motor neuropathy
2. Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP)
3. Neonatal sepsis
4. Prophylactic use of IVIg in prematures.

<u>Second line therapy option</u>

5. Severe myasthenia gravis
6. Dermatomyositis

B.III. Posology issues:

7. Are the current dosage recommendations and targeted trough levels of IgG given in the cSPC still adequate for PID patients? Recent literature suggests higher doses should be used, if patients develop more than 2 severe infections/year despite standard therapy.
8. Recent literature recommends a single 2 g/kg dose for Kawasaki's syndrome rather than two or more doses over 2-5 days.
9. Recent literature recommends 2 g/kg dose for Guillain-Barré syndrome given over 2-5 days (Hughes, et al. Intravenous Immunoglobulin for Guillain-Barré syndrome. The Cochrane Database of Systematic Reviews, 2004: Issue 1 CD002063).

B.IV General review of contraindications, precautions and warnings, and undesirable effects taking into account the revision of the SPC Guideline.

The purpose of this Expert Meeting is to address these issues; the conclusions will be taken into account in the revision of the Note for Guidance and the corresponding core SPC.

3. Time and location of the expert meeting

Wednesday 5 July 2006 – Thursday 6 July 2006, 2 day expert meeting. The expert meeting will be immediately followed by a restricted 1 day meeting of BPWP with co-opted experts to discuss the conclusions of the meeting and to propose revisions of the current CHMP guidance on IVIg.

Location: EMEA

4. Organisation of the meeting

Organisation by the EMEA with advice from the BPWP.

5. Participants

BPWP Rapporteurs for the expert meeting:
J. Kerr
P. Laitinen-Parkkonen
C. Ratignier

Invited speakers/chairpersons
D. Brasseur (CHMP Chairman)

A. BUZYN LÉVY

H. Chapel
R. W. I. Cooke
P. Gajdos
L. Mouthon
R. Hughes
S. Kaveri
B. Keller-Stanislawski (PhVWP member)
A. Nascimento
D. Pongratz (Apologies sent)
P. Rossi (PEG member)
I. van Schaik
M. Seppänen
R. Thorpe

P. VOLKERS (EWP MEMBER)

BPWP Chairman, M. Haase, and Members

CHMP, PhVWP, EWP, PEG, COMP and SAWP members who wish to participate

EMEA Speakers:
N. Seigneuret
G. Silvester

Representatives invited from:
IPFA: International Plasma Fractionation Association
PPTA: Plasma Protein Therapeutics Association
IPOPI/EPPIC: International Patient Organisation for Primary Immunodeficiencies/European Patients Primary Immunodeficiency Collaboration
Patients' representative for myasthenia gravis
EURORDIS: European Organization for Rare Diseases
ESID: European Society for Immunodeficiencies
EFIS: European Federation of Immunological Societies
EFNS: European Federation of Neurological Societies
ENMC: European Neuromuscular Centre
Cochrane Neuromuscular Disease Review Group

Other authorities with an interest in this topic who wish to participate (e.g. FDA, WHO, Japan, Australia)

L. R. Pierce (FDA)

EMEA Secretariat Support
S. Domingo, K. Balzan, B. Neugebauer, G. Silvester, L. Svobodova

EXPERT MEETING ON Revision of core SPC and Note for Guidance for human normal Immunoglobulin for intravenous administration Guidance for human normal Immunoglobulins

Questions to be addressed by the Experts

1. Should IVIg be assessed as a group or individual products?

    1.1. Cover the principles that we currently use and the regulatory basis for this.

    1.2. Difficulties for rare conditions of requiring data on each individual product.

2. Indications:

    2.1. What data do we have to justify the new indications?

    2.2. What data requirements are needed for each new indication? To include consideration of statistics for small populations.

    2.3. Is there a need for the revision of established indications and posology?

    2.4. Should additional data be requested in paediatric patients in indications already established?

3. Is there a need for harmonisation in the requirements?

EXPERT MEETING ON REVISION OF CORE SPC AND NOTE FOR GUIDANCE FOR HUMAN NORMAL IMMUNOGLOBULIN FOR INTRAVENOUS ADMINISTRATION

WEDNESDAY 5 JULY 2006 – THURSDAY 6 JULY 2006

AGENDA

Day 1, Session 1, Introduction to the topic Chair: **M. Haase** Rapporteur: J. Kerr, EMEA: G. Silvester		
	Presentations	
1	Introduction, welcome and purpose – **M. Haase** (10 min) Declaration of conflict of interests – All (5 min)	09.30-09.40 09.40-09.45
2	Regulatory framework – **G. Silvester** (15 min)	09.45-10.00
3	IVIg guideline - relevance of the ITP model – **J. Kerr** (15 min)	10.00-10.15
3a	IVIg guideline – regulatory perspective – **G. Silvester** (5 min) Questions on 3 and 3a (5 min)	**10.15-10.20** 10.20-10.25
4	US FDA approach to data requirements for IVIg indications other than PID – **L. R. Pierce** (10 min)	10.25-10.35
5	Statistical approach – **P. Volkers** (15 min) **QUESTIONS (5 MIN)**	10.35-10.55
	Coffee Break	10.55-11.15
6	Paediatric Committee/Scientific Advice Working Party (SAWP)/CHMP roles – **N. Seigneuret** (15 min) Questions (5 min)	11.15-11.35
7	**Discussion (30 min)**	11.35-12.05
	<u>*Points to be addressed:*</u> *7.1 Should IVIg be assessed as a group or as individual products?* *The following should be taken into account with respect to this question:* • *The principles that are currently used in the CHMP guideline and their regulatory basis.* • *Difficulties for rare conditions of requiring data on each individual product.* *7.2 IVIgs used in other areas have proved beneficial and the possible inclusion of other indications may reflect current clinical practice. What data requirements are needed for each new indication?* *In the case of rare indications, there is the question of the extent of clinical data needed before the indication can be considered as “established” for IVIgs. This includes consideration of statistics for small populations.* *7.3 Idiopathic (autoimmune) thrombocytopenic purpura (ITP):* *Is there is a need to distinguish between modified and non-modified IVIg products in the criteria for proof of efficacy and safety in ITP? (Products that are Fc-modified have shown to be of limited efficacy in ITP.) – comments* **R. Thorpe**	
Day 1, Session 2, **General aspects**, Chair: **L. Mouthon**, BPWP Rapporteur: C. Ratignier, EMEA: S. Domingo		
	Presentations	
1	General IVIg mechanisms and impact of autoantibodies – **S. Kaveri** (20 min) Questions (5 min)	**12.05-12.30**
2	French view – **L. Mouthon** (20 min) Questions (5 min)	12.30-12.55

	Lunch Break	**12.55-13.55**
3	US FDA requirements for PID studies **– L. R. Pierce** (15 min) **QUESTIONS (5 MIN)**	13.55-14.15
4	Primary immunodeficiency (PID) – **M. Seppänen** (20 min) **QUESTIONS (5 MIN)**	**14.15-14.40**
5	Chronic lymphocytic leukaemia (CLL) – **H. Chapel** (20 min)	14.40-15.00
5a	CLL **– M. Anderesi**, PPTA (5 min) Questions on 5 and 5a (5 min)	15.00-15.10
6	Allogeneic bone marrow transplantation (ABMT) – **A. Buzyn Lévy** (20 min)	15.10-15.30
6a	ABMT – **Dr. I. Andresen**, PPTA (5 min) Questions on 6 and 6a (5 min)	**15.30-15.40**
	Coffee Break	**15.40- 16.00**
7	Safety aspects of IVIg – **B. Keller-Stanislawski** (20 min) Questions (5 min)	16.00-16.25
8	PPTA perspective – **F. Fabbrizzi** (10 min)	16.25-16.35
9	IPFA perspective **– T. Waegemans** (10-15 min) Questions on 8 and 9 (5 min)	16.35-16.55
10	EPPIC/IPOPI Patients' perspective **– D. Watters** (10 min)	16.55-17.05
11	**Discussion** (45 min)	17.05-17.50
	Including introductory remarks from **H. Chapel** *Points to be addressed:* *11.1 Do the currently recommended studies, "established indications" and their respective posologies require modification to more adequately reflect current clinical practice with IVIgs?* *11.2 Primary immunodeficiency (PID) study requirements:* *Is there scope for harmonisation of CHMP recommendations for pharmacokinetic, efficacy and safety studies in PID patients with FDA draft recommendations? (FDA draft guidance for comment purposes only published in November 2005.)* *11.3 Are the current dosage recommendations and targeted trough levels of IgG given in the cSPC still adequate for PID patients? Recent literature suggests higher doses should be used, if patients develop more than 2 severe infections/year despite standard therapy.* *11.4 Chronic lymphocytic leukaemia (CLL)* *What is the current role of IVIg in CLL treatment in view of the wide spectrum of antibiotics that has been developed to combat infectious complications? It is argued in a recent retrospective study (Hensel, Br J Haematol. 2003 Aug; 122(4):600-6) that disease activity and pre-treatment are the major risks for infectious complications in CLL.* *11.5 Allogeneic bone marrow transplantation (ABMT)* *What is the current role of IVIg in ABMT treatment? In recent studies the use of prophylactic IVIg in ABMT has been questioned. In one study there was no benefit over placebo.* *11.6 General review of contraindications, precautions and warnings, and undesirable effects taking into account the revision of the SPC Guideline.*	
	End of Day 1	

Day 2, Session 1, Neurological aspects, Chair: **R. Hughes**, BPWP Rapporteur: J. Kerr, EMEA: G. Silvester		
	Presentations	
1	Introduction to inflammatory neuropathies – **R. Hughes** (5 min) Key aspects to be considered – **J. Kerr** (5 min)	8.30-8.35 8.35-8.40
2	Multifocal Motor neuropathy (MMN) – **I. van Schaik** (20 min) Questions (10 min)	8.40-9.10
3	Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) – **I. van Schaik** (25 min)	9.10-9.35
3a	CIDP – **E. Rentz**, PPTA (10 min) Questions 3 and 3a (5 min)	9.35-9.50
	Coffee break	**9.50-10.10**
4	Myasthenia gravis (MG) – **P. Gajdos** (25 min) Questions (5 min)	10.10-10.40
5	Myasthenia gravis – view of patients organisation – **R. Ricciardi** (20 min) Questions (5 min)	10.40-11.05
6	Dermatomyositis and other forms of myositis – **D. Pongratz** (Apologies sent) (25 min) **QUESTIONS (5 MIN)**	11.05-11.35
7	**Discussion** (50 min)	11.35-12.25
	<u>*Points to be addressed:*</u> *7.1 Based on a review of current evidence, is there sufficient data to consider the following indications "established" for IVIgs? If not, what additional data would be needed?* **MMN** *CIDP* <u>*Second line therapy option:*</u> *Severe myasthenia gravis* *Dermatomyositis* *7.2 Recent literature recommends 2 g/kg dose for Guillain-Barré syndrome given over 2-5 days (Hughes, et al. Intravenous Immunoglobulin for Guillain-Barré syndrome. The Cochrane Database of Systematic Reviews, 2004: Issue 1 CD002063).* ***R. Hughes to start discussion.***	
	Lunch break	**12.25-13.25**
Day 2, Session 2, Paediatric aspects, Chair **D. Brasseur** , BPWP Rapporteur: P.Laitinen-Parkkonen, EMEA: S.Domingo		
	Presentations	
1	IVIg and infections in children with HIV despite of HAART and prophylactic antimicrobial treatment (10 min) IVIg in children with known immunodeficiency syndromes and new diseases (10 min) Use of IVIg as immunoreplacement after selective immunoablative regimens (5 min) Kawasaki posology (5 min) **P. Rossi** Questions (10 min)	13.25-14.05
2	Neonatal sepsis – Controlled trials of immunoglobulins in neonatal sepsis. Prophylactic use IVIg in preterms. **R. W. I. Cooke** (20 min) Questions (5 min)	14.05-14.30

3	Paediatric neurological syndromes – **A. Nascimento** (20 min) Questions (5min)	14.30-14.55
	Panel discussion 60 min Panel members: **R. W. I. Cooke** **H. Chapel** **H. Gajek, PPTA** **A. Nascimento** **P. Rossi** **P. Strengers, IPFA** **EPPIC/IPOPI**	14.55-15.55
4	*Points to be addressed:* *4.1 Do the currently recommended studies, "established indications" and their respective posologies require modification to more adequately reflect current clinical practice with IVIgs in paediatric patients?* *4.2 For each IVIg product, should additional data be requested in paediatric patients in indications already established?* *4.3 Paediatric AIDS:* *Should the indication be modified to define more precisely the current use of IVIg in paediatric AIDS?* *4.4 Recent literature recommends a single 2 g/kg dose for Kawasaki's syndrome rather than two or more doses over 2-5 days.* *4.5 Based on a review of current evidence, is there sufficient data to consider the following indications "established" for IVIgs? If not, what additional data would be needed?* • *Neonatal sepsis* • *Prophylactic use IVIg in preterms.* *4.6 Based on a review of current evidence, what conclusions can be reached on IVIg use in paediatric neurological syndromes?* *4.7 General discussion on paediatric trial design as part of small populations approach.*	
Summary of the workshop J. Kerr, C. Ratignier and P. Laitinen-Parkkonen (15 min)		15.55-16.10
Close of Meeting: Prof. Haase		16.10-16.15

Coffee available after close of meeting

ANNEX III

LIST OF PARTICIPANTS

EXTERNAL EXPERTS

A. Buzyn Lévy
Hôpital Necker Enfants maladies, France

H. Chapel
Oxford Radcliffe Hospital, John Radcliffe Site, United Kingdom

R. W. I. Cooke
Liverpool Women's Hospital, University of Liverpool, United Kingdom

P. Gajdos
Hôpital Raymond Poincaré, France

R. A. Hughes
Guy's, King's and St. Thomas' School of Medicine Department of Clinical Neurosciences, United Kingdom

S. Kaveri
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L. Mouthon
Hôpital Cochin, France

A. Nascimento
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M. Seppänen
Helsinki University Central Hospital, Finland

FOOD AND DRUG ADMINISTRATION. USA

L. R. Pierce
Food and Drug Administration, Div. of Hematology, USA

BPWP MEMBERS, EXPERTS AND OBSERVERS

M. Haase
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D. Apele-Freimane
Zāļu valsts aģentūra, Latvia

N. C. Cestafe
Agencia Española del Medicamento y Productos, Spain

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AGES PharmMed / Bundesamt für Sicherheit im Gesundheitswesen, Austria

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G. Medgyesi
Országos Gyógyszerészeti Intéset, National Institute of Pharmacy, Hungary

A. Moraru
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CHMP, COMP, PhVWP, EWP, PEG, SAWP AND OTHER REGULATORY EXPERTS AND OBSERVERS

D. Brasseur
Service Public Féderal Santé Publique, Sécurité de la Chaîne alimentaire et Environnement, Belgium

R. Elbers
Bundesinstitut für Arzneimittel und Medizinprodukte, Germany

B. Keller-Stanislawski
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P. Rossi
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R. Thorpe
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OBSERVERS

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PATIENT ORGANISATION

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International Patient Organisation for Patients with Primary Immunodeficiencies, UK

F. Houÿez
European Organisation for Rare Diseases, Plateforme Maladies Rares, France

R. Ricciardi
Associazione Italiana per la lotta contro la Miastenia, Italy

D. Watters
International Patient Organisation for Patients with Primary Immunodeficiencies, UK

D. Andersen
Guillain-Barré Syndrome Support Group, UK

IPFA

T. Evers
International Plasma Fractionation Association, The Netherlands

IPFA INDUSTRY

P. Strengers
CAF-DCF cvba, Belgium

R. Cuperus
Sanquin, The Netherlands

F. Rossi
Laboratioire Francais du Fractionnement et des Biotechnologies, France

T. Waegemans
Laboratoire Francais du Fractionnement et des Biotechnologies, France

C. Dash
Bio Products Laboratory, United Kingdom

E. Gascoigne
Bio Products Laboratory, United Kingdom

PPTA

Ch. Waller
Plasma Protein Therapeutics Association, Belgium

I. von Hoegen
Plasma Protein Therapeutics Association, Belgium

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M. Anderesi
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E. Rentz
Biotest AG, Germany

F. Fabbrizzi
Kedrion SpA, Italy

H. Gajek
Baxter BioScience, Austria

E. Bastida	Grifols
H-P. Schwarz	Baxter
B. Fiorention	Kedrion
S. Haag	Octapharma
C. Hope	Talecris
O. Zenker	ZLB Behring

EMEA SECRETARIAT

S. Domingo

K. Balzan

B. Neugebauer

A. Weyersberg

I. Rager

N. Seigneuret

G. Silvester

L. Svobodova