22 July 2010
EMA/CHMP/BPWP/604687/2009
Committee for Medicinal Products for Human Use (CHMP)

# Overview of comments received on the guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg) (EMA/CHMP/BPWP/94033/2007, rev. 2 formerly CPMP/BPWG/388/95 rev. 2)

Interested parties (organisations or individuals) that commented on the draft document as released for consultation.

| Stakeholder no. | Name of organisation or individual |
|---|---|
| 1 | CBG-MEB NL |
| 2 | International Plasma Fractionation Association (IPFA) |
| 3 | Medical Advisory Board of the Guillain-Barré Syndrome Support Group |
| 4 | International Patient Organisation for Primary Immunodeficiencies (IPOPI) |
| 5 | Associazione Italiana Miastenia Onlus |
| 6 | Talecris Biotherapeutic GmbH |
| 7 | Plasma Protein Therapeutics Association (PPTA) |
| 8 | CSL Behring AG, Bern, Switzerland |

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# 1. General comments – overview

| Stakeholder no. | General comment (if any) | Outcome (if applicable) |
|---|---|---|
| 1 | These modifications (Guideline + SmPC) are in line with new medical developments and reflect current clinical practice. | N/A |
| 2 | No general comments | N/A |
| 3 | The guideline on core SMPC for IVIg omits chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and multifocal motor neuropathy (MMN) from its recommendations. We consider this inappropriate for the reasons given below. | See outcome statements below |
| 4 | We ask that the following points be noted and considered before publication of the final document. We have consulted our Medical Advisory Panel in addition to seeking consumer views. In addition we urge that urgent attention be given to subcutaneous infusion of Ig as this is growing area of usage throughout Europe. | The BPWP is aware of the increased s-c use of immunoglobulins and will be addressing any upcoming issues in a further revision of the SCIG/IMIG Guideline and core SmPC. |
| 5 | Treatment with IVIg, in our experience of Association in close contact with patients and close contact with the "Ambulatory for the treatment of Myasthenia Gravis" in the "Azienda Ospedaliera Universitaria Pisana", is effective as well as in myasthenic crisis, even in the chronic treatment of MG in all those conditions that are poorly responsive to other specific therapies.<br>We send, attached to this letter, the witness/testimonials of Italian patients who have used or still use intravenous immunoglobulin treatment on a monthly, bimonthly or otherwise periodical basis, for long periods with great benefits.<br>The 113 testimonials attached have been collected in 3 months (May-July 2009) exclusively through the website of our Association. There are therefore many more patients who benefit from treatment and hope that immunoglobulin will remain in the therapeutic indications of Myasthenia Gravis. | We greatly appreciate the feedback from the Associazione Italiana Miastenia Onlus and would like to take the opportunity to thank all the patients for their testimonials. This contribution makes it very clear that fortunately patients are well organised and aware of the decision processes in this area. The testimonials also show that there are considerable differences in time intervals between treatments with IVIg. Possibly more precise data could be extracted from registries. If data of 113 patients can be effectively collected in one EU country in 3 months then it is deemed feasible for the plasma producing industry to encompass these (and other) patients in a well designed confirmatory study to address some of the open issues e.g. long-term treatment, benefit over cortisone for exacerbations, possible study in cortisone resistant/intolerant patients. |
| 6 | The current situation for CIDP is different from the situation with the other auto-immune disorders mentioned in the draft revision of the | It is recognised that with the ICE study Talecris has provided a large extension to the existing knowledge base. As the |

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| | guideline (multifocal motor neuropathy (MMN) and myasthenia gravis exacerbations), since the CIDP indication has been included in the SmPC for Gamunex.<br>The Gamunex License has recently been updated to include the CIDP indication after a variation to the marketing authorization was approved, in which data showing the efficacy of Gamunex in CIDP based on the ICE study were presented. This study was conducted as a randomized, placebo controlled complete phase III clinical study. Clinical data showing efficacy in CIDP have now been included in the license for Gamunex.<br>Since Talecris has demonstrated that it is feasible to conduct a clinical study with IVIg in the treatment of CIDP, it does not seem appropriate in our view to only require confirmatory data for other IVIgs. | evidence base increases, one could argue that confirmatory data of a smaller scope may suffice i.e. if other companies can show that similar results can be obtained with their products, then, depending on the outcome and timeframe of the trial, this data may contribute to addressing the issue of interchangeability (or class effect). |
| 7 | N/A | N/A |
| 8 | General comments have been transferred to Specific Comments on IVIg Guideline | See below. |

# 2. Specific comments on guideline text

## *2.1. 1st consultation*

| Line no. | Stakeholder no. | Comment and rationale; proposed changes | Outcome |
|---|---|---|---|
| 47 | 7 | **Comments:**<br>"failure" of antibody production could be misinterpreted with "failing" or "no" antibody production.<br><br>**Proposed change (if any):**<br>Replace "failure" with "impaired" | Accepted. |
| 62-65 | 6 | **Comments:**<br>The inclusion of CIDP in this list is in our view no longer appropriate, due to the approval of the IVIg Gamunex for the indication CIDP. Consequently it does not seem appropriate to only require confirmatory data for other IVIgs. (also see General Comment above)<br><br>**Proposed change (if any):**<br>"For other auto-immune disorders (in particular multifocal motor neuropathy (MMN) and myasthenia gravis exacerbations) confirmatory data are required, see 7.3.5.<br><br>In other indications ,relevant clinical data are required" | Not accepted<br><br>Prior to the ICE trial the CIDP landscape was such that the 6 randomised controlled trials (from 1993-2001) with ~ 170 adult patients showed indications of efficacy but were difficult to compare as different disability scales were used and the studies had other methodological issues (timing of the primary endpoint; the definition criteria for CIDP).<br><br>Five different IVIg brands were used.<br><br>Now the database has been increased by the methodologically sound ICE study by Talecris with a further IVIg (Gamunex). Therefore, it was considered likely that other IVIgs may obtain similar results but would have to offer some confirmatory proof with a given product. |
| 69 | 7 | **Comments:**<br>"Expectedness" is not to be determined for every Adverse Event.<br><br>**Proposed change (if any):**<br>Remove *"expectedness"* and include a cross-reference | Not accepted.<br><br>Expectedness of an AE is listed in most trial protocols. |

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| | | to section 7.4.1. | |
| 79-80 | 7 | **Comments:**<br>The sentence “Therefore it is no longer considered appropriate to use clinical trials to investigate viral safety with regard to enveloped viruses” should be removed since this is considered “state of the art” knowledge since several years.<br><br>**Proposed change (if any):**<br>Remove the sentence | Accepted. |
| 92 | 7 | **Comments:**<br>The cited cross-reference to 6.1.2.1. is not correct.<br><br>**Proposed change (if any):**<br>N/A | Accepted and corrected. |
| 143 | 2 | **Comments:**<br>To be in accordance with line 291, paediatric age groups should be clarified.<br><br>**Proposed change (if any):**<br>"IgG trough levels should be studied in patients with primary immunodeficiency syndromes (PID), whereby 20 of these should be children **or adolescent** with an age distribution representative of this patient population **in the disease."** | Partly accepted. "IgG trough levels should be studied in patients with primary immunodeficiency syndromes (PID), whereby 20 of these should be children **or adolescents** with an age distribution representative of this patient population**."**<br><br>(PID has already been mentioned in the sentence; therefore the wording “in the disease” is redundant.) |
| 145 | 2 | **Comments:**<br>IgG trough levels should be assessed at steady state. In order to clarify this point, the bracket should be placed at the end of the sentence.<br><br>**Proposed change (if any):** | Partly accepted. Reference to half-lives was omitted |

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| | | The IgG trough levels obtained should be assessed prior to each infusion over a period of 6 months, ~~(6.5 times the expected half life)~~ starting after 5-6 administrations of the product **(6.5 times the expected half life)**. | |
| 152-153 | 2 | **Comments:**<br>"…by repeated blood sampling after approximately 5-6 administrations of the product until the day before the next infusion…"<br><br>**Proposed change (if any):**<br>The last part of this section would be better if the 'last' sample was immediately before the next infusion (*i.e.* a trough level) because trough levels are requested for each infusion, elsewhere. | Accepted.<br><br>**Change:**<br><br>"…by repeated blood sampling after approximately 5-6 administrations of the product until immediately before the next infusion…" |
| 153 | 2 | **Comments:**<br>Inclusion of 20 adult patients with primary immunodeficiency for a full PK program could be difficult in this relative rare disease.<br><br>Possibilities to reduce PK population size in case of low dispersion results could be proposed.<br><br>**Proposed change (if any):**<br>Add "**In case of preliminary low dispersion results on other PK parameters study, a reduction of this sub-population size could be acceptable**." | Not accepted. PID prevalence ranges from 1-4/100 000. In the EU this would imply 5000 -20 000 patients and 3000 – 12 000 in the USA. It is deemed feasible to collect data from 20 patients. |
| 156 | 7 | **Comments:**<br>We understand that we have to study either group A OR group B and not both (treated and naive). The wording could be rephrased for clarity.<br><br>**Proposed change (if any):** | Partly accepted.<br><br>The wording has been changed to clarify this:<br><br>Pharmacokinetic data set can be derived from patients with primary immunodeficiency syndromes (PID) who are either in |

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| | | "Pharmacokinetic data should be derived from patients with primary immunodeficiency syndromes (PID) who are either in group A) already stabilised on IVIg treatment or in group B) naïve to IVIg treatment" | group A) already stabilised on IVIg treatment or in group B) naïve to IVIg treatment or the set can contain both patient groups. |
| 189 | 2 | **Comments:**<br>"….quality of life."<br><br>While QoL is important to patients, this proposed assessment only makes sense in the context of a study for naïve patients. To assess possible changes in QoL for patients on one IVIg who transfer to an alternative IVIg would be unlikely to show much difference once steady state had been reached on the new/modified product.<br><br>**Proposed change (if any):**<br>N/A | Not accepted. It was decided not to incorporate QOL as this will not provide reliable data in an open label study |
| 189 | 7 | **Comments:**<br>The parameter "quality of life" is very broad and hence should be specified in order to provide some direction on which to focus e.g. SF36 as general questionnaire.<br><br>**Proposed change (if any):**<br>Include details for "quality of life". | Not accepted.<br><br>It was decided not to incorporate QOL as this will not provide reliable data in an open label study. |
| 216<br>(§ N$^{o}$ 7.3.3) | 2 | **Comments:**<br>There is difficulty to obtain the required 30 patients for a study in ITP especially with a baseline platelet count below or equal to 20x $10^{-9}$/l.<br><br>A doubling of the numbers from the current Note for Guidance is severe, especially for organisations already embarked on the trial as previously specified. | Partly accepted.<br><br>ITP occurs with an incidence of approximately 5-10 per 100,000 persons per year among adults and approximately 4-5 per 100,000 per year in children. In the EU (27 states) this would imply an incidence of 25000. It is therefore considered feasible to obtain data in 30 patients. |

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| | | Discussions with others involved in similar ITP studies, indicate that it takes 4-6 months on average to recruit one adult per centre once the centre has been initiated for the trial.<br><br>We propose to stay with 15 patients as required in the current Note for Guidance and we ask for clarification of the maximal baseline platelet value for inclusion.<br><br>Usually, patients with low platelet count receive medication before falling to the value of 20x $10^{-9}$/l.<br><br>Also low platelet counts are difficult to measure accurately so the word “about” is welcome. Current treatment guidelines advise against treating just the ‘platelet count’<br><br>Does this statement allow entry to the study for patients with evidence of bleeding although platelet counts might be slightly >20 x $10^{9}$/L?<br><br>We propose to set a maximal value to 30x $10^{-9}$/l.<br><br>**Proposed change (if any):**<br>An open study with the investigational IVIg should be performed in ~~30~~ **15** chronic adult ITP patients with a baseline platelet count ~~of about 20 x $10^{9}$/l~~. **<30 x $10^{-9}$/l.** | The ITP study design has been altered to encompass the recommendations by the International Working Group (IWG) on Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children. This has been released for a 2nd public consultation (see below). |
| 217 | 7 | **Comments:**<br>The baseline platelet count should be adapted to “below” 50 x $10^{9}$/l and bleeding signs” instead of “about 20x $10^{9}$/l”<br><br>The platelet count alone is not decisive. Bleeding signs | Partly accepted.<br><br>The study design has been altered to encompass the recommendations by the International Working Group (IWG) on **Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura** |

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| | | in patient with more than 20x $10^9$/l (e.g. 50 x $10^9$/l) require therapy.<br><br>**Proposed change (if any):**<br>Replace “about” with “below” 50 x $10^9$/l and bleeding signs or patients with platelets about 20x $10^9$/l” | **of adults and children.** |
| 239 | 7 | **Comments:**<br>The efficacy parameter “relationship to any new haemorrhages to platelet count” needs to be clarified, maybe rewording would help.<br><br>**Proposed change (if any):**<br>N/A | Partly accepted<br><br>The ITP study design has been altered to encompass the recommendations by the International Working Group (IWG) on Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children |
| 246 | 7 | **Comments:**<br>The sentence “response rates and mean duration (...)”is contradictory to the general approach of the Guideline and the core SmPC.<br><br>**Proposed change (if any):**<br>Remove sentence | Accepted. |
| 255-258 | 6 | **Comments:**<br>Based on the ICE-study results for both short and long-term efficacy, the indication for CIDP has been included in the IVIg Gamunex license.<br><br>Therefore, the statement (lines 256-259) is no longer appropriate and should be amended as indicated below.<br><br>CIDP, on the contrary, should be covered by section 7.3.6 (lines 266 – 271) (also see comment above).<br><br>**Proposed change (if any):**<br>Published literature indicates a positive effect of IVIgs | Not accepted.<br><br>See comment above |

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| | | in some auto-immune disorders in particular multifocal motor neuropathy (MMN) and myasthenia gravis exacerbations. | |
| 261-263 | 7 | **Comments:**<br>The nature of the confirmatory data for Chronic Inflammatory Demyelinating Polyneuropathy (CIDP), severe Myasthenia gravis (MG) & Multifocal Motor Neuropathy (MMN) should be defined in discussions between industry and EMEA.<br>**Proposed change (if any):**<br>N/A | Accepted, a Stakeholders Meeting was arranged.<br>However, specific suggestions from industry to help clarify the issue were not received during the Stakeholders Meeting. Individual proposals by companies are welcomed, also through the Scientific Advice procedure. |
| 294-295 | 7 | **Comments:**<br>Requirement for a separate safety evaluation of excipients should be clarified: does that mean that clinical data have to be evaluated (in any case) concerning the safety of excipients?<br>**Proposed change (if any):**<br>"A separate safety evaluation of the excipients **in case this is indicated by non-clinical data**, including a summary of the non-clinical and literature data, should be (...)" | Partly accepted.<br>It is unclear whether all critical excipients can actually reveal their potential dangers in non-clinical studies (e.g. fructose, maltose etc.), literature data (in humans) might be equally important.<br>**Change:**<br>A separate safety evaluation of the excipients should be provided, which should encompass a summary of the non-clinical and literature data. |
| 305 | 1 | **Comments:**<br>only line 305 - Coomb's test<br>**Proposed change (if any):**<br>Direct antiglobulin test (DAGT) | Partly accepted. The wording **Direct antiglobulin test (DAT)** is the more precise term; however Coombs' test is an old and well established term<br>**Proposed change**:<br>Direct antiglobulin test (DAT; direct Coombs' test) |
| 309-311 | 2 | **Comments:**<br>"In addition, the applicant should review other areas | Partly accepted. |

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| | | where further study of IVIg in the paediatric population is needed and include within the plan a proposal to study at least one of these areas."<br><br>It is not clear to what this refers.<br><br>Does this refer to different indications to those formerly investigated, to other indications for which the licence has been granted on the basis of PID or ITP, or to a specified age-group within the children/adolescent range?<br><br>**Proposed change (if any):**<br>N/A | **Proposed change:**<br><br>Where a paediatric investigation plan is required in order to comply with the Paediatric Regulation (EC) No 1901/2006, the applicant should provide a plan that includes the recommendations described in this guideline for the paediatric population. |
| 312 | 7 | **Comments:**<br>The Guideline should refer to the ICH Q5E Comparability Guideline in which it is clearly stated that "determination of product comparability can be based solely on quality considerations (...) if the manufacturer can provide assurance of comparability through analytical studies as suggested in this document". Therefore the draft Note for Guidance clearly contradicts the referenced comparability Guideline.<br><br>**Proposed change (if any):**<br><br>We believe that this section should be revised in order to have a common understanding and include the stepwise approach of ICH Q5E. | This section has been revised. |
| 313-318<br>(§ N° 8) | 2 | **Comments:**<br>The adjective "Significant" should be clarified.<br><br>Paragraph 8 should be read in conjunction with the | Partly accepted.<br><br>This section has been re-written |

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| | | NOTE FOR GUIDANCE ON BIOTECHNOLOGICAL/BIOLOGICAL PRODUCTS SUBJECT TO CHANGES IN THEIR MANUFACTURING PROCESS CPMP/ICH/5721/03.<br><br>Demonstration of comparability is a sequential process, beginning with quality studies (limited or comprehensive) and supported, as necessary, by PK study and or, clinical study. If a manufacturer can provide evidence of comparability through physico-chemical and biological studies, then PK or clinical studies with the post-change product are not warranted.<br><br>In other cases, additional non-clinical and/or clinical data will be required.<br><br>The need, of PK and clinical comparability studies will be determined on a case-by-case basis in consideration with the nature of the change, the potential impact on the molecule structure and on the final product profile.<br><br>Proposed change (if any):<br>Add **"This paragraph should be read in conjunction with the NOTE FOR GUIDANCE ON BIOTECHNOLOGICAL/BIOLOGICAL PRODUCTS SUBJECT TO CHANGES IN THEIR MANUFACTURING PROCESS CPMP/ICH/5721/03."**<br><br>Changes in the manufacturing procedures may lead to significant changes in the product and may thereby alter the structure of the immunoglobulin and/or its activity. | |

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| | | Biological and pharmacokinetic data are the key elements to evaluate activity and safety of IVIg preparations.<br><br>Demonstration of comparability is a sequential process, beginning with quality studies and supported, as necessary, by PK study and or, clinical study. If a manufacturer can provide evidence of comparability through physico-chemical and biological studies, then PK or clinical studies with the post-change product are not warranted.<br><br>In other cases, additional non-clinical and/or clinical data will be required.<br><br>The need for PK and clinical comparability studies will be determined on a case-by-case basis in consideration with the nature of the change, the potential impact on the molecule structure and on the final product profile."<br><br>If a significant impact on the activity of the immunoglobulin, **based on comparability results on biological data in a first step, or PK comparability in a second step** cannot be excluded, data on ~~pharmacokinetics and~~ safety in PID patients and efficacy and safety in ITP patients should also be provided with the application. | |
| 315 | 7 | **Comments:**<br>The very general sentence "Biological and pharmacokinetic data are the key elements to evaluate activity and safety of IVIg preparations." provides no help in this section referring to "Change". | This section has been revised. |

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| | | **Proposed change (if any):**<br>The sentence should be deleted or moved to the very beginning of the section. Ideally, the ICH Q5E reference should be included. | |
| 316-317 | 7 | **Comments:**<br>The sentence needs to be revised in order to reflect the Comparability Guideline. "If a significant impact on the activity of the immunoglobulin cannot be excluded, data on pharmacokinetics and safety in PID patients and efficacy and safety in ITP patients should also be provided with the application."<br><br>**Proposed change (if any):**<br>Reword the first sentence: "For the evaluation of changes and their significance the approach of the ICH Q5E Guideline on "Comparability of Biotechnological Products" should be followed. | This section has been revised. |
| 324 | 7 | **Comments:**<br>N/A<br><br>**Proposed change (if any):**<br>Include further information in order to reflect ICH Q5E. Insert an additional sentence:<br><br>*"If the biological data are different from the parent product, the effects on pharmacokinetics and safety in PID patients and efficacy and safety in ITP patients should also be investigated."* | This section has been revised. |
| 326 | 7 | **Comments:**<br>"A limited set of pharmacokinetic data in PID patients for the changed product is required. ...This | This section has been revised. |

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| | | encompasses:"<br>In accordance with ICH Q5E non-clinical studies should be considered e.g. a comparative PK study.<br><br>**Proposed change (if any):**<br>*"A limited set of pharmacokinetic data is required, e.g. a PK study in PID patients for the changed product. This encompasses:"* | |
| 333<br>(§ N° 8) | 2 | **Comments:**<br>A lower PK population size could be acceptable according to the type of change of manufacturing process and the expected impact.<br><br>Proposed change (if any):<br>Add<br><br>**"A lower PK population size could be acceptable according to the type of change of manufacturing process and the expected impact."** | Not accepted.<br><br>This section has been re-written.<br><br>It is difficult to conceive that PK data from an even smaller population (<20) would convey meaningful results with regard to comparability of the product within the IVIG product class. Given the prevalence of PID it is deemed reasonable to obtain PK data in 20 patients. |
| 335-336 | 2 | **Comments:**<br>“If the biological, pharmacokinetic and safety data show no change from the parent product: For replacement therapy no further efficacy or safety data would be required.”<br><br>Does this mean that the study in PID does not need to be as long as 12 months for all patients, so that once the full number of PK assessments has been collected (after 5-6 infusions) from the last patient, the study could end?<br><br>**Proposed change (if any):** | Partly accepted.<br><br>This section has been re-written and includes the idea that the extent of clinical data to be provided has to be judged on a **case-by-case basis** depending on the anticipated impact of the changes and could vary from a pharmacokinetic trial comparing “pre-change” versus “post-change” product up to the full clinical data set as outlined for a new product.<br><br>If a PK trial is required it would be in a limited set of 20 adult PID patients by assessing plasma concentration-time curve, half-life, AUC, Vd, Cmax, Tmax, and elimination rate constant(s) through repeated blood sampling after approx. the 5-6 administrations of the changed product until immediately |

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| | | N/A | before the next infusion. These PK parameters should be compared to data obtained with the predecessor product. |
| 335-345 | 7 | **Comments:**<br>Lines 335 to 339 are in contradiction to lines 315 to 318 and ICHQ5E. We question the requirement to conduct a clinical trial when there is no significant impact observed.<br><br>**Proposed change (if any):**<br>Delete line 335 to 339. Position lines 340 to 342 after line 345 | This section has been revised. Section 2.5 of ICH Q5E states that “Additional evidence from nonclinical or clinical studies is considered appropriate when quality data are insufficient to establish comparability.” Therefore, the requirement on a case-by-case basis for an ITP study, since the biological rationale for efficacy in ITP is not completely elucidated, is consistent with ICH Q5E. |
| | 8 | **Comments:**<br>1. After a positive evaluation of the information from the literature and from experts in the medical fields of rare neuroimmunological disorders as multifocal motor neuropathy (MMN), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) and myasthenia gravis (MG), exacerbations/crisis in which IVIgs are currently used off-label, we like to express our disappointment with the published revision of the above guidelines for IVIgs.<br><br>**Proposed change (if any):**<br>N/A | 1. We acknowledge the disappointment felt by the company; however, it has also been disappointing for the agencies that until the recent (ICE and PRIVIG) trials no robust clinical studies were performed by the companies that would have allowed granting or rejecting a MA for the off-label uses. |
| | 8 | **Comments:**<br>2. As summarised below IVIg has been shown to be effective and safe in many controlled clinical studies in these diseases. Therefore we believe that post marketing commitments are sufficient to provide product specific confirmatory data. | 2. Due to a number of shortcomings in the clinical trials in MG, MMN and CIDP (before the ICE trial) the data gave rise to various questions that would be more clearly answered by further well designed studies. In addition companies have not performed head-to-head studies comparing PK and efficacy in the established indications, thus it remains difficult to extrapolate the possible efficacy of one product to another. |

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| | | **Proposed change (if any):**<br>N/A | Therefore post-marketing commitments are not deemed sufficient, rather confirmatory trials are deemed a more convincing way forward. |
| | 8 | **Comments:**<br>3. From a clinical perspective it is not clear how the request for product specific clinical trial data would improve the knowledge on IVIg treatment of patients suffering from any of the above neurological diseases.<br><br>**Proposed change (if any):**<br>N/A | 3. The more well-designed trials that are performed with different IVIg brands in the individual indications the more likely an indication can be regarded as being established. Furthermore, data on dosing, duration of therapy, subgroups that respond and possibly the underlying mechanisms of IVIg in the individual pathologies etc. could be collected. This would greatly improve the knowledge base. |
| | 8 | **Comments:**<br>4. Given that patient numbers in all concerned indications are low, the participation in multiple clinical trials would be a substantial burden for the patients which seems not to be balanced with the request to generate new scientific evidence.<br><br>**Proposed change (if any):**<br>N/A | 4. See comment 7. (example MMN) We disagree with the idea that further trials would be a “burden”, as patients would be receiving a study drug and would be gaining security from a greater evidence base after the trial outcome (if positive) is in the public domain. |
| | 8 | **Comments:**<br>5. From a regulatory perspective it is further not discernible, why applications for line extensions based on well-established medicinal use in accordance with Annex 1 of Directive 2001/83/EC should not be possible. The directive explicitly recognises that product specific confirmatory data from medicinal products with “well-established efficacy and an acceptable level of safety” are not needed. Bibliographic applications should suffice. | 5. Well-established medicinal use has a specific legal meaning as set out in Article 10a of Directive 2001/83/EC as amended “…in well-established medicinal use within the Community for at least ten years, with recognised efficacy and an acceptable level of safety in terms of the conditions set out in Annex I.”, This legal basis is not appropriate for CIDP, MMN and MG exacerbations. |

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| | | By requiring product specific confirmatory data it is foreseeable that the availability of IVIg's that can be used within the label will be limited.<br><br>**Proposed change (if any):**<br>N/A | |
| | 8 | **Comments:**<br>6. Referring to the report of the EMEA expert meeting on the revision of the core SmPC and the clinical note for guidance (NfG) for human normal immunoglobulin for intravenous administration (IVIg) from January 24, 2008, there is sufficient data to consider the neuroimmunological disorders as MMN and CIDP and myasthenia gravis exacerbations/crisis as "established" for IVIg as first line therapy option and severe myasthenia gravis as second line therapy and no additional data are needed to demonstrate efficacy and safety.<br><br>**Proposed change (if any):**<br>N/A | 6. The experts felt that for the most part IVIgs were interchangeable and that there was sufficient evidence for the indications mentioned. The industry has not refuted or supported the concept of interchangeability. Seen from a quality point of view the different products are not interchangeable. What exact implications the individual quality differences have on the clinical outcomes (e.g. immunmodulation and side-effects) has not been studied (head-to-head studies are lacking).<br><br>Apart from these considerations the experts also acknowledged that the trials had a number of methodological shortcomings. |
| | 8 | **Comments:**<br>7. For **MMN** there are study results (4 randomised controlled trials, 4 different IVIg products: Azuley et al., 1994; van den Berg et al.,1995; Federico et al., 2000; Lèger et al., 2001) and meta-analyses consistently showing an advantage for all parameters, for the secondary endpoint "increase in muscle strength" the effect was significant (p=0.0005). EMEA expert R. Hughes commented that disability scales are not designed for the upper limb disabilities seen in MMN | 7. For one of the rarest indications namely MMN the lifetime prevalence is 1:100 000 – this would imply that within the EU there would be approx. 5000 patients and in the USA another 3000. RCTs in MMN so far have encompassed 34 suitable patients. From the Cochrane review the literature search revealed 94 case reports or case series and over 70 reviews. It is difficult to say which patients have been included in the more recent retrospective studies and reviews and whether there is any overlap. |

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| | | and this could be the reason for the failure to show a significant benefit for disability. Thus the experts at the EMEA expert meeting on July 5-6, 2006 considered that there is sufficient evidence for MMN as a first line indication for IVIg treatment.<br><br>Additional data gathered from the literature after the EMEA expert meeting have been taken into account during the revision process. Two studies have shown progressive motor deterioration in most patients, correlated with electrophysiological signs indicative of axonal degeneration, while a third study (*Cros et al.*,2006) 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.<br><br>In a recent retrospective study (Delmont et al., 2007) 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.<br><br>In another review by Delmont et al., 2006 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 | From the Cochrane Review 2008 (Van Schaik):<br><br>*Implications for practice*<br><br>*Limited evidence from randomised controlled trials shows a non-significant trend towards improvement in disability after intravenous immunoglobulin compared with placebo. There was a significant improvement in muscle strength.*<br><br>*Implications for research*<br><br>***More research is needed** to discover whether intravenous immunoglobulin improves disability and is cost-effective* |

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| | | treatment.<br><br>In addition the EFNS/PNS guidelines consider IVIg as the first line treatment (level A recommendation) when disability is sufficiently severe to warrant treatment.<br><br>**Proposed change (if any):**<br>N/A | |
| | 8 | **Comments:**<br>8. For CIDP IVIg 6 randomised controlled studies were analyzed 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 (Dyck et al., 1994; Hughes et al., 2001; Vermeulen et al., 1993; Mendell et al., 2001). CIDP also responds to corticosteroids and plasma exchange. Thus, the experts considered that there is sufficient evidence to regard IVIg treatment as a first line treatment option for CIDP.<br><br>Additional data gathered from the literature after the expert meeting have been taken into account during the revision process: A RCT study included 117 patients was conducted in 31 centres in 10 countries worldwide. The analysis of the data has shown a short-term and long-term efficacy and safety of IGIV-C for CIDP (Hughes et al., 2008).<br><br>**Proposed change (if any):**<br>N/A | 8. The CIDP landscape has changed since the addition of the well-designed ICE study and the large population base it encompassed. For one, it has proved that such trials are feasible in rare disorders. However, the BPWP recognises that given the enlarged database, confirmatory data would not have to cover such a large population as in the ICE study, nevertheless consideration should be given to the scope of the confirmatory dataset (sample size, dose, time frame), the choice of the neurological scale and clinically meaningful differences within the chosen scale, the comparator arm/ or lack of comparator and the wash-out period of previous medication and/or stable co-medication. In essence this applies to the other neurological disorders. |

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| | 8 | **Comments:**<br>9. For myasthenia gravis the experts considered that there is 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. Additional data gathered from the literature after the EMEA expert meeting have been taken into account during the revision process.<br><br>In the article "Guidelines for the treatment of autoimmune neuromuscular transmission disorders" by Skeie GO et al, 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).<br><br>**Proposed change (if any):**<br>N/A | 9. The objective of the Cochrane Review on MG *"was to examine the efficacy of intravenous immunoglobulin for treating acute exacerbations or for chronic long-term, persistent myasthenia. We identified six randomised controlled trials, all of which investigated short-term benefit.*<br><br>*For treating exacerbations, one RCT of IVIg vs placebo demonstrated the efficacy. Another trial showed no significant difference between IVIg and plasma exchange.*<br><br>*For moderate or severe myasthenia gravis there is no evidence from randomised controlled trials or from other trials to determine whether intravenous immunoglobulin improves function or reduces the need for steroids. There is insufficient evidence to favour intravenous immunoglobulin over corticosteroids in moderate exacerbations".*<br><br>Therefore a number of points remain unresolved (long-term treatment, dosing, benefit over cortisone, possible study in cortisone resistant/intolerant patients). |
| | 8 | **Comments:**<br>10. Based on the review of current evidence from literature and EMEA experts opinion at the EMEA expert meeting, there is sufficient data to consider the indications as MMN, CIDP and myasthenia gravis exacerbations/crisis as established for IVIgs for first line treatment. | 10. The EMEA expert meeting did indeed provide a substantial basis for considering the indications MMN, CIDP and MG exacerbations as highly promising candidates. Despite large numbers of case reports and reviews very few studies were actually taken into consideration by the analyses in the Cochrane Reviews and even these showed a number of methodological flaws. It was therefore felt by the BPWP that to place these indications on a firmer evidence base additional |

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| | | We believe that no additional confirmatory data from pre-licensure trials are needed for IVIg to be used in these rare neuroimmunological disorders.<br><br>**Proposed change (if any):**<br>N/A | confirmatory data would be of essence and in the process of doing so the issue of interchangeability (or possible class effect) of immunglobulins may be addressed. |

## *2.2. 2nd consultation (ITP part)*

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| General | 1 | **Comments:**<br>The section on ITP is based on the recommendations by Rodeghiero F. *et al.* Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. Blood. 2009;113:2386-2393.<br><br>The draft Guideline states that the term idiopathic thrombocytopenic purpura has been exchanged for primary immune thrombocytopenia according to the recommendations of the above mentioned International Working Group. However the term, defined in the IWG publication of Rodeghiero *et al* "to indicate the absence of any obvious initiating and/or underlying cause" has not been defined in the Guideline.<br><br>For example the IWG proposes using the term secondary ITP for amongst others ITP (HIV-associated). It should be clear that the population to be investigated only concerns patients with primary ITP. | Not accepted<br><br>It is general practice to define such syndromes or disorders as "primary" in which an obvious initiating and/or underlying cause is not known. |

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| | | **Proposed change (if any):**<br>N/A | |
| General | 2 | **Comments:**<br>We welcome the move to make more consistent the clinical studies performed in ITP. There will, undoubtedly, be several studies ongoing at the present time with IVIg in ITP. There are some significant changes in these proposed guidelines which affect entry criteria and assessment of responses. A clear message needs to be sent urgently to the industry so they can determine whether changes need to be made to ongoing protocols and analysis of studies.<br>**Proposed change (if any):**<br>None, except consideration of above perhaps by separate message. | Accepted.<br>No changes need to be made to the ongoing protocols. Protocols submitted after CHMP adoption of the IVIg Guideline will obviously have to be encompass the new study design<br>See also section on 'Implementation' in Procedure for EU guidelines and related documents within the pharmaceutical legislative framework (EMEA/P/24143/2004 Rev. 1 corr).<br>http://www.ema.europa.eu/pdfs/human/regaffair/2414304en.pdf |
| 273 | 2 | **Comments:**<br>Please see item on ITP (7.3.3), indicating that there should be a separate efficacy study with ITP patients: children are also necessary for such study. It seems a heavy burden, taking into account that ITP is mentioned as an established use. In 7.3.4. it is stated that ITP is considered an established use, even though no explicit study is performed. This seems a contradiction.<br>**Proposed change (if any):**<br>N/A | Not accepted.<br>The text already states "An open, study with the investigational IVIg should be performed in 30 chronic (> 12 months duration) **adult** ITP patients with a baseline platelet count of <30 x $10^9$/l."<br>Section 7.3.4 states that efficacy of the IVIg product in PID and ITP should be established. |
| 280 | 2 | **Comments:**<br>On this line there are two points which highlight the above general comment: (a) the number of patients is | Accepted. |

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| | | now 30 rather than the 15 in the current guideline. This will affect the protocol of some studies and the need to refer to Ethics Committee to increase numbers; (b) the duration of ITP before categorisation of 'chronic' has been doubled and again will affect ongoing protocols with a potential need to change the protocol and resubmit for Ethics Committee approval.<br><br>**Proposed change (if any):**<br>None, except consideration of above general point. Studies in ITP are difficult because of the fluctuating platelet counts making it difficult to enrol patients below the threshold. The newer prophylactic agents further reduce the patient population available for studies with IVIg. | No changes need to be made to the ongoing protocols. Protocols submitted after CHMP adoption of the IVIg Guideline will obviously have to be encompass the new study design |
| 281 | 2 | **Comments:**<br>Again there is a significant change in an entry criterion. Although this relaxes this criterion (<30 x $10^9$/L from <20 x $10^9$/L), there will need to be a protocol amendment and Ethics Committee approval.<br><br>**Proposed change (if any):**<br>None, except consideration of above general point. This change will help to balance the difficulty in recruitment for future studies. | See above |
| 285-288 | 2 | **Comments:**<br>"to minimize the risk of clinically significant bleeding."<br><br>The article by Rodeghiero F. et *al.* (Blood March 2009) mentioned that there is a "limitation" which "is represented by the lack of validated tools to assess | Accepted. |

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| | | bleeding risk".<br><br>**Proposed change (if any):**<br><br>"… ~~to minimize the risk of clinically significant bleeding~~"<br><br>"…to minimize the risk of bleeding considered as clinically significant by the investigator". | |
| 292-293 | 2 | **Proposed change (if any):**<br>"Corticosteroids are permitted if the patient is either on long-term stable dose of corticosteroids or the platelet count falls below 30 x 109 /l again **after IVIg treatment**, but should not to be given as a pre-treatment to alleviate potential tolerability problems." | Accepted. |
| 299 | 2 | **Comments:**<br>The period of 7 days may be too long to confirm response (R) because IVIg does not necessarily provide a long-lasting effect and the data could suggest R on Day X, but has dwindled before DX+7. These criteria have not been used in previous studies so to try to compare data from a new study with historical data will be confounded by the different criteria used.<br><br>The use of a repeat count after one day, for NR or loss of response, will not be easy or helpful to patients, who | Not accepted.<br><br>In our experience in most studies submitted over the past 10 years, platelet counts have been checked regularly within the first 7 -10 days after IVIg administration, followed by sampling approx. every 5-7 days thereafter for ~3-4 weeks. For responders Tmax has generally been reached at Day 2-7, the platelet counts have generally not dwindled to <50 x $10^9$ /l before Tmax +7. So it is expected that platelet counts would rise above 30 x $10^9$ /l earlier and fall below 30 x $10^9$ /l later than for the former threshold of 50 x $10^9$ /l.<br><br>Patients with very low, non-rising or falling platelet counts would have to be checked in any case – the one day time |

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| | | may be otherwise reasonably well.<br><br>**Proposed change (if any):**<br>Rely on a single platelet count for R and CR and use serial counts to estimate duration of response. | frame is considered feasible. |
| 299-301 | 2 | **Comments:**<br>Brackets are not closed<br><br>**Proposed change (if any):**<br>Platelet counts should be confirmed on at least 2 separate occasions (at least 7 days apart when used to define complete response (CR) and response (R)**)** or 1 day apart when used to define no response (NR) or loss of response. | Accepted, but text subsequently modified. |
| 300-301 | 1 | **Comments:**<br>It is not clear how the measurement of platelet count a second time within 7 days fits into the definitions of (complete) response. Is it the intention to consider that the conditions for (complete) response have not been met if the specified platelet count has not been reached within 7 days or falls below 100 x $10^9$/l or 30 x $10^9$/l within 7 days?<br><br>The IWG publication (Table 3) gives a time to peak response with IVIg of 2 to 7 days.<br><br>**Proposed change (if any):**<br>**S**pecifiy that a complete response or response must be reached within 7 days. | Partly accepted<br><br>In our understanding of the article it is part of the definition of response to have two separate measurements taken 7 days apart to confirm the response value.<br><br>So in a typical setting a patient would achieve a platelet count >30 x $10^9$/l within 2-3 days and keep this level at least until Day 9-10 (i.e. + 7 days) after which it may dwindle below 30 x $10^9$/l. (see comment above)<br><br>The text has been modified for greater clarity. |
| 302-306 | 2 | **Comments:**<br>There is no time frame specified for these categories. Reference to Table 3 of the Blood publication upon | Partly accepted.<br><br>The article by Rodeghiero is referenced here. |

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| | | which these changes are modelled should provide a reasonable assessment, however, either a reference needs to be made here or the appropriate data on IVIg from that Table reproduced here.<br><br>**Proposed change (if any):**<br>Consider a reference to the Blood article, Table 3, or explain in words in the text associated with these lines. | |
| 302-310 | 2 | **Comments:**<br>The proposed draft includes several efficacy criteria without hierarchy for the assessment. Primary and secondary endpoints need to be defined. We propose the primary efficacy criteria be the raise in platelet count. Moreover, the efficacy is dose dependent. To prevent systematic higher dosage regimen during clinical trial aimed at achieving platelet count above 100 x 109 /l and not representative of the current practice nor possible lower dosages, the efficacy assessment should be focused on the following primary criterion (see below the proposed change)<br><br>**Proposed change (if any):**<br><br>Primary criterion :<br>"Number and % of patients with R : platelet count ≥30 x $10^9$ /l and at least 2-fold increase the baseline count and absence of bleeding"<br><br>Secondary criteria :<br>• Number and % of patients with CR : platelet count >100 x 109 /l and absence of bleeding<br>• Time to response: time from starting treatment to time of achievement of CR or R (Late responses not | Not accepted<br><br>It is acknowledged that platelet count (response rate) is one of the main criteria of the study, however, duration of response was also deemed very relevant. (see next comment by the same stakeholder ("what good am I doing my patient and for **how long**?") By putting a hierarchy on the various outcomes or creating co-primary endpoints (response and duration) the study design (numbers of patients) and statistics would need altering. It was therefore decided to leave the listing of endpoints as it is |

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| | | attributable to the investigated treatment should not be defined as CR or R)<br>• Number and % of patients with NR: platelet count < 30 x 109/l or less than 2-fold increase of baseline platelet count or bleeding<br>• Number and % of patients with loss of CR or R: platelet count below 100 x 109/l or bleeding (from CR) or below 30 x 109/l or less than 2-fold increase of baseline platelet count or bleeding (from R) | |
| 314-315 | 2 | **Comments:**<br>The expression of individual patient's mean and median values is not very clinically worthwhile because these values depend upon the numbers of times platelet counts were measured and over what duration of time. The estimate of duration (for CR and R) is a much better and clinically relevant estimate (i.e. what good am I doing my patient and for how long?).<br><br>Although not very understood clinically, a better single value per patient would be an estimate of the $AUC_{0-X}$ with last value carried forward, if there are missing values (usually because of poor response). The X in the AUC refers to a stipulated post treatment day, e.g Day 28 or Day 35 for example.<br><br>**Proposed change (if any):**<br>Omit these summaries. Consider the possibility of an alternative single measure, or rely on CR, R and duration as the most clinically relevant objective parameters of efficacy. | Not accepted<br><br>By asking for mean and median values, standard deviation and ranges should also be given, thereby recording minimum and maximum values, which are considered clinically relevant. In addition this allows to judge a given product within the setting of other IVIgs, by obtaining mean (SD) and median (range) values.<br><br>Individual patient results (especially minimum values) are deemed the clinically more meaningful data compared to AUC. |