EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

21 October 2010
EMA/CHMP/BPWP/375734/2010
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg) (EMA/CHMP/BPWP/94038/2007 rev. 3 formerly CPMP/BPWG/859/95 rev. 3)

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. *(See cover page)*	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. 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. 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.

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
6	The current situation for CIDP is different from the situation with the other auto-immune disorders mentioned in the draft revision of the guideline (multifocal motor neuropathy (MMN) and myasthenia gravis exacerbations), since the CIDP indication has been included in the SmPC for Gamunex. 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. 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.	It is recognised that with the ICE study Talecris has provided a large extension to the existing knowledge base. As the 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 IVIg Core SmPC

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
74	7	**Comments:** The IgA Content is stated in microgram/ml. Such a change would require revision of the SmPC/PIL and labelling causing unnecessary regulatory actions and associated costs without any obvious benefit. **Proposed change (if any):**	Not accepted. The SmPC Guideline states that the "use of decimal points should be avoided where these can be easily removed (e.g. 250 microgram, not 0.25 mg). For safety reasons, micrograms and millions (e.g. for units) should always be spelled out in full

		Keep to previous wording "mg/ml"	rather than be abbreviated".
76	7	**Comments:** The inclusion of the sentence " Produced from the plasma of human donors." does not provide additional information and could be misleading – there is no other source for plasma. **Proposed change (if any):** Delete sentence	Not accepted. In the SmPC Guideline it is stated that the biological origin of the active substance should be mentioned and this is the recommended wording.
88	4	**Comments:** There was general agreement that a broad classification was better than naming (and omitting) conditions. However, what about sub-classes? This document will be used as a handbook by private health insurers across Europe. **Proposed change (if any):**	Not accepted. (From Prof. Mikko Seppänen): *"IgG subclass deficiency and selective IgA deficiency can currently not be recommended to be added to the established indications*". *"For adult selective antibody deficiency (SAD) (with or without selective 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".*
92	7	**Comments:** "Primary immunodeficiency syndromes with ***failure*** of antibody production", should be replaced by : "Primary immunodeficiency syndromes with ***impairment*** of antibody production", in order to avoid a misunderstandable interpretation. (see also line 47,Draft CPMP/BPW/388/95 rev. 2) **Proposed change (if any):** N/A	Accepted. **Proposed change:** Primary immunodeficiency syndromes with impaired antibody production (see section 4.4). In section 4.4 it is stated that "IVIg is not indicated in patients with selective IgA deficiency where the IgA deficiency is the only abnormality of concern"

110-113	6	**Comments:** CIDP should be removed from the list of auto-immune indications. (also see general comment above, and refer to general comment on Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg) (CPMP/BPW/388/95 rev.2)) **Proposed change (if any):** *[For product specific auto-immune indications (e.g. multifocal motor neuropathy (MMN), ~~chronic inflammatory demyelinating polyradiculoneuropathy (CIDP),~~ myasthenia gravis exacerbations) and other product specific indications – see Guideline on the Clinical Investigation of Human Normal Immunoglobulin for Intravenous Administration (IVIg) CPMP/BPWG/388/95 rev. 2]*	Not accepted. See above.
115	4	**Comments:** Trough levels appear to be on the low side – our Medical Advisory Panel (MAP) advice that this should be at least 5g/l if not 5-6g/l. The data provided will be used by those more anxious to control expenditure than improve the quality of life for the patient. **Proposed change (if any):** N/A	Accepted. 5-6 g/l is accepted In addition further increases are possible: *Trough levels should be measured and 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.*
127	2	**Comments:** "The recommended starting dose is 0.4-0.8 g/kg followed by at least 0.2 g/kg/month given in divided doses every one to four weeks." May we have the rational of the recommendation to divide starting dose every one to four weeks. The	Accepted. **Proposed changes:** The recommended starting dose is 0.4-0.8 g/kg given once, followed by at least 0.2 g/kg/month given every three to four weeks.

		guideline Clinical Investigation of Human Normal Immunoglobulin for Intravenous Administration CPMP/BPWG/388/95 Rev. 2, currently in consultation doesn't mention this administration mode. **Proposed change (if any):** N/A	
139	7	**Comments:** The nature of the pneumococcal should be clarified with respect to conjugated or polysaccharide vaccine. **Proposed change (if any):** N/A	Clarified Pneumovax (a polysaccharide vaccine) is the only vaccine licensed for adults.
152	3	**Comments:** In addition it recommends that the dose of IVIg used in Guillain-Barré syndrome be 0.4g/kg/day for three to seven days, whereas the universally used regime is 0.4g/kg/day over five days. We know of no evidence to support the dose of 0.4g/kg/day being used over seven days. **Proposed change (if any):** Posology for GBS: 0.4g/kg/day over 5 days	Accepted.
159	7	**Comments:** We don't understand the rationale to list the paediatric population separately again in the column named "indication"? In addition the paediatric population is mentioned in line 162 again. **Proposed change (if any):** Remove the sentence from the table.	Accepted.
187-191	2	**Comments:**	Not accepted. On 2nd March 2001 a "Benefit-risk evaluation of fructose and sorbitol-containing solutions for parenteral use"

		"This medicinal product….and may be fatal." This warning for products containing fructose or sorbitol is contrary to advice received by BPL from Medicines Control Agency at an early stage in the development of a new IVIg. The advice given after consultation with the Belgian authorities and others at EU level was as follows: "I now have EU feedback on the issue you've raised. It would appear that as iv gamma globulins are used as stat injection the sorbitol content is not thought to present a significant risk. I hope this helps." [e-mail dated 12 March 2002 from Panos Tsintis (panos.tsintis@mca.gsi.gov.uk) to Dr Clive Dash at BPL. The question to which this was the reply was sent on 10 September 2001 seeking information on a 'Reminder' in Current Problems in Pharmacovigilance 2001;27:13 entitled 'Fructose and sorbitol containing parenteral solutions should not be used". The reply from MCA prompted a further e-mail from Dr Dash to MCA pointing out that sorbitol was used in a licensed IVIg so was the difference between this type of product and iv solutions for parenteral nutrition one of dosage. Inherited fructose intolerance is rare (except in indigenous Greenlanders). There have been no reports of events related to this genetic abnormality from IVIg as far as is known to Grifols and BPL. In addition, sorbitol is categorised as GRAS (Generally Regarded As Safe). Because of this background, the proposed statement is considered excessive (see next comment).	was performed by Daniel Brasseur and Xavier Kurz following the death a an 18 month old child who had been administered a fructose-containing solution (i.v). In the literature up to 1993 23 cases had been reported, whereof 17 were fatal (73%). Not all 17 case reports gave information on dosing. However, three adult patients died after receiving ~25- 50g of sorbitol (in one case an infusion over 10 h). The report concludes: *An excessive amount of fructose or sorbitol is not necessary for a fatal outcome.* Death typically occurred within 3-10 days after the first fructose or sorbitol administration as a consequence of severe renal and liver failure. The Grifols product contains 50 mg sorbitol/ml and 50 mg IgG/ml. E.g. a 10 kg child with Kawasaki's disease would require 20 g Flebogammdif (i.e. 400 ml) which in turn would mean that it would receive 20 g of intravenous sorbitol. This is approaching the fatal doses for adults. **Therefore despite the extreme rarity of fructose intolerance the warning statement is deemed adequate and should remain as it is suggested in the draft revision.** The GRAS status refers to oral intake of sorbitol.

		Proposed change (if any): N/A	
188-189	2	**Comments:** "Patients with rare hereditary problems of fructose intolerance should not take this medicine." This is already covered in Section 4.3 Contraindications. In this section (4.4) of Warnings it would be better to caution about use in babies and young children. A suggested rewording is as follows: "Hereditary fructose intolerance (see 4.3), although rare, may not yet have been diagnosed in babies and young children, so special caution is required when considering a product containing fructose or sorbitol (metabolised to fructose) for them as it may be fatal." The current proposed text of lines 187-191 becomes redundant as the advice is covered by that in 4.3 and the suggested alternative for 4.4 mentioned. These lines relate to excipients in different products and cover fructose/sorbitol, maltose, glucose. In this section there should be mention of sucrose as an excipient for completeness. The warning about sucrose is contained in lines 259-262. **Proposed change (if any):** It is suggested that the paragraph (lines 258-263) is brought forward to the start of section 4.4. The adverse effects of sucrose are well described, have actually occurred and have actually been fatal for some patients. It therefore has a more important place than comments on the other excipients.	Partly accepted. Proposed Changes This medicinal product contains XXmg of sorbitol /fructose per ml as an excipient. Patients with rare hereditary problems of fructose intolerance should not take this medicine In babies and young children hereditary fructose intolerance may not yet be diagnosed and may be fatal, thus, they should not receive <sorbitol><fructose>-containing solutions**.** In other patients in case of inadvertent administration and suspicion of fructose intolerance the infusion has to be stopped immediately, normal glycemia has to be re-established and organ function has to be stabilized by means of intensive care. Mention of sucrose has been included at the start of 4.4.

207 and 209	2	**Comments:** "Certain adverse reactions may occur more frequently - in patients with hypo- or agammaglobulinaemia with or without IgA deficiency" In the case of hypo- or agammaglobulinaemia, it is probable that any increased rate of ADRs is related to underlying infection (clinical or subclinical) rather than the PID conditions *per se*. This is not clear from this warning statement. **Proposed change (if any):** N/A	Partly accepted. The sentence has been deleted, as in the 3 centralised products it does not seem to be the case that adverse reactions occur more frequently in PID pts. > 90% of PID and ITP pts had AEs, the proportion of pts. with related AEs was actually higher for ITP.
234	7	**Comments:** The second sentence "They can occur in very seldom cases of IgA deficiency with anti-IgA antibodies" implies that only IgA deficiency leads to true hypersensitivity reactions. This is not correct. **Proposed change (if any):** We recommend to delete the sentence and to include the sentence from section 4.8 line 331 ("Rarely human normal immunoglobulins may cause a sudden fall in blood pressure and, in isolated cases, anaphylactic shock, even when the patient has shown no hypersensitivity to previous administration") or cross-refer to section 4.8.	Not accepted. The risk of hypersensitivity in patients with anti-IgA antibodies needs to be included. A sentence similar to the one in section 4.8 line 331 is already included here.
255	4	**Comments:** We are concerned that the reference to age could be used as a basis against infusion. **Proposed change (if any):** N/A	As this is under **Warnings and Special Precautions for Use** (Subheading Acute Renal Failure) we do not view it as a basis against infusion *per se*, rather the treating physician should prudently weigh the possible risk of ARF in high risk patients.

279-280	7	**Comments:** The prefix "allo-" is not reflecting the situation correctly, the interference relates in general to antibody testing. **Proposed change (if any):** Delete "allo-"	Accepted.
282-285	2	**Comments:** "Transmissible agents…" This is an appropriate position for this warning statement, but there is a repetition in Section 4.8 (lines 343-345). It is unnecessary to have the same statement in two places. **Proposed change (if any):** Perhaps in 4.8 there could be a cross reference such as "For information on potentially transmissible agents, see 4.4."	Not accepted. Cross reference to the warning statement guideline is included in 4.4 and 4.8 so that the text needed in each section is taken from that guideline. This is for practical purposes so that if the text is revised at any time this only has to be done in the guideline and not in each core SmPC.
294	4	**Comments:** Live attenuated vaccines are contra-indicated in the majority of PID – including all antibody production defects **Proposed change (if any):** N/A	Not accepted. This section would also apply to the immunomodulatory disorders and not only to PID patients – therefore it would be of relevance for this population
304	4	**Comments:** Pregnancy: there is confusion here – establishment of safety versus clinical experience. Our MAP makes the point that replacement should be continued, even increased, between infusions – or higher doses being necessary to maintain trough levels **Proposed change (if any):**	Not accepted. As the dosing goes by weight –this would presumably cover the increase necessary in pregnancy

		N/A	
324	4	**Comments:** Although no studies have been done about driving or using machines most patients follow normal life-style activities after infusion of Ig and no accidents have been reported in many thousands of patients for many years in many countries across the world. The statement at line 324 could raise doubts in the minds of some... **Proposed change (if any):** N/A	Partly accepted. As side-effects can be dizziness, nausea, headache the wording has been revised to be more informative.
343-345	2	**Comments:** See above (lines 282-285). See previous comment. **Proposed change (if any):** N/A	Not accepted. Reason as above.
420-421	2	**Comments:** "Where applicable, the amount of albumin added as a stabiliser should be stated…" It is not clear why albumin has been singled out here. The general SmPC guidance has removed quantitation of excipients in 6.1. However, it would be appropriate to give the quantities of the key stabilisers such as sucrose, maltose, glucose, fructose, sorbitol, L-proline *etc* here so that there is a single place to find this information, as it is considered important for prescribers **Proposed change (if any):** A cross reference in section 4.4, for example, could be given to 6.1.	Not accepted The European Pharmacopoeia requests for the labelling that the amount of albumin should be stated. Section 2 should include quantitative information on excipients that have a recognised action or effect Section 4.4. includes the warnings on the excipients. Section 4.8. encompasses adverse reactions of excipients. Section 6.1. is to include the entire list of excipients.

N/A	3	**Comments:** The conclusion in the core SMPC concerning CIDP is in contradiction to the report of the EMEA expert meeting on the revision of the core SmPC and note for guidance for IVIg (document reference EMEA/CHMP/BPWP/361857/2006) held at EMEA in July 2006 and published on 24th January 2008. At that meeting the evidence from six randomised controlled trials was summarised and in a meta-analysis performed in the Cochrane review clear short-term benefit on IVIg was shown.(1) Since then, a further large trial confirmed the short-term benefit of IVIg and showed for the first time that maintenance treatment also had long-term benefit.(2) The evidence has been updated in the latest update of the Cochrane review.(3) It is possible that this new evidence was not considered by the EMEA in the preparation of the core SMPC. In **multifocal motor neuropathy**, at the same EMEA expert meeting in July 2006, van Schaik reported the meta-analysis from his Cochrane review of four randomised controlled trials which showed that IVIg induced a short-term improvement in strength and a trend towards improvement in disability.(4) The evidence for MMN is less strong than for CIDP but it is universally used in neurological practice for this condition because no other treatment is available. Human immunoglobulin is recommended as a first line treatment option for CIDP by all the national and international guidelines which have considered the problem and as the only treatment available for MMN.(5-9)	Partly accepted The EMA 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 confirmatory data would be of essence and in the process of doing so the issue of interchangeability (or possible class effect) of immunoglobulins may be addressed. **MMN** From the Cochrane Review 2008 (Van Schaik): *"Implications for practice* *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.* *Implications for research* ***More research is needed** to discover whether intravenous immunoglobulin improves disability and is cost-effective*" Individual products can include these indications in their SmPC based on confirmatory data with the product. The core SmPC will be kept under review with respect to the accumulating data.

		Proposed change (if any): In view of the cumulative strength of the evidence we ask you to include CIDP and MMN in the core SMPC for human immunoglobulin. (Reference list supplied by GBS advisory group is omitted in this overview for the sake of brevity)	
			New: Proposal for package leaflet Include INFORMATION FOR MEDICAL OR HEALTHCARE PROFESSIONALS ONLY, as dosing and method of administration is not always mentioned specifically in the package leaflet. It is of utmost use to the treating physician to have easy access to this information within the package leaflet, as the SmPC is not always readily available