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SCIENCE MEDICINES HEALTH

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Human Medicines Evaluation

Overview of comments received on 'the guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg)' (EMA/CHMP/BPWP/94038/2007 Rev. 5)

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

Stakeholder no.	Name of organisation or individual
1	CSL
2	IPOPI
3	M de Visser
4	Prof. Dr. Benedikt Schoser Friedrich-Baur-Institute, Dep. of Neurology Munich, Germany
5	Biotest
6	Grifols
7	IPFA
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1. General comments – overview

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3	In addition to Professor Schoser's comments I should like to add the following: In the Cochrane Review by Gordon et al. on treatment in dermatomyositis and polymyositis (see attachment) the trial by Dalakas et al. on treatment resistant DM showed a significant improvement of muscle strength over a period of 3 months and hence IVIg should be mentioned for that indication. In addition, evidence is accumulating from cohort studies (and also a recent ENMC workshop) that patients with immune mediated necrotizing myopathies need IVIg - sometimes as first line therapy - in at least one-third of the cases. Gordon PA, Winer JB, Hoogendijk JE, Choy EHS. Immunosuppressant and immunomodulatory treatment for dermatomyositis and polymyositis. Cochrane Database of Systematic Reviews 2012, Issue 8. Art. No.: CD003643. DOI: 10.1002/14651858.CD003643.pub4. Watanabe Y, Uruha A, Suzuki S, et al. J Neurol Neurosurg Psychiatry 2016;87:1038–1044. http://dx.doi.org/10.1136/	It is agreed that IVIG is used off-label for DM. However, the evidence from RCTs remains sparse There is only one small DM study with IVIG - this is not considered sufficient for an indication to be taken into the coreSPC. http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD003643.pub4/pdf *In Dalakas 1993 (15 participants), although an activities of daily living (ADL) score was assessed, the results in the two groups were not reported systematically and statistical comparison between the two groups was not reported. A significant improvement in the NSS (measured in 13 participants) was reported for IVIg (44.1 (SD8.2) pretreatment and 51.4 (SD6.0) at three months) but not for the placebo group (45.9 (SD 9.0) pretreatment and 45.7 (SD 11.3) at three months). The NSS is a score based on 20 activities, each scored from zero to three, where three signifies no impairment and zero severe impairment.* *Cochrane: Two small trials, one of IVIg (Dalakas) in dermatomyositis, the other of etanercept in dermatomyositis suggested that they are beneficial. More RCTs are needed.*
4	I am missing here the inclusion of the disease termed myasthenia gravis. IVIG is one of the most used rescue treatments in acute	It is agreed that IVIG is frequently used off-label for MG exacerbations and that some Neurological Societies are in

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	myasthenia gravis. **References** Cochrane Database Syst Rev. 2012 Dec 12;12:CD002277. doi: 10.1002/14651858.CD002277.pub4. Intravenous immunoglobulin for myasthenia gravis. Gajdos P1, Chevret S, Toyka KV. Guidelines for treatment of autoimmune neuromuscular transmission disorders. Skeie GO, Apostolski S, Evoli A, Gilhus NE, Illa I, Harms L, Hilton-Jones D, Melms A, Verschuuren J, Horge HW; European Federation of Neurological Societies. Eur J Neurol. 2010 Jul;17(7):893-902.	favour of IVIG use in MG exacerbations. From a regulatory point of view the data base is still somewhat weak. See table below for interpretation of Cochrane Review. It is considered premature to include this indication to the established indications as yet. Two larger placebo-controlled trial with IVIG are ongoing One non-controlled open-label study in MG crisis is ongoing A pilot phase and a Phase II study with an SCIG are ongoing. One SCIG study has been terminated by sponsor due to difficulty enrolling at site. These results should be awaited.
	Interpretation of Cochrane Review 2012 Highlighted in yellow are methodological shortcomings, in green are methodologically sound studies	

Year	PI	Design	Bias	No.	Type of MG	Verum	Comparator	Outcome
2011	Barth	RCT	None	84	Worsening	Gamunex 2g/kg	5x PLEX	Equal efficacy at Day 14
2007	Zinman	p-c	None	51	Exacerbation	IVIg 1 g/kg for 2 days	Placebo	IVIG effective at Day 14 and 28
2005	Gajdos	2 doses IVIG	No true comparator	173	Exacerbation	1 g/kg of IVIG	IVIg 2 g/kg	No difference Day 15
2002	Schuchardt	RCT	100 pts required, 33 included. Never published	33	Exacerbation	IVIg 30 g/d for 5 days	MP 1 - 1.5 mg/kg for 14 days	?
2002	Wolfe	RCT, p-c	88 participants required/15 included	15	mild or moderate MG	IVIg 1 g/kg for 2 days (6 pts)	5% albumin for 2 days (9 pts)	no significant difference in primary or secondary outcomes between 2 groups
2001	Ronager	RCT, X-over	Random sequencing not sufficient No. of pts not justified	12	stable moderate or severe MG	Group 1: IVIg 0.4 g/kg for 5 days and 16 weeks later 5 PE	Group 2: opposite schedule	At Week 1 and 4 wk no difference between 2 treatments
1997	Gajdos	RCT	not blinded	87	Exacerbation	IVIg 2 g/kg + IVIg 1.2 g/kg	3x PLEX	Equal efficacy at Day 15

p-c = placebo controlled, pts + patients, PI = principle investigator

8	The current text:	Added

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	Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent bacterial infections, ineffective antibiotic treatment and either proven specific antibody failure (PSAF)* or serum IgG level of <4 g/l. PSAF= failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and polypeptide antigen vaccine. Observations: 1. In SID after transplantation we observe not only bacterial infections but also viral and even severe fungal infections. 2. Antibody response to polysaccharides use to be associated with control of bacterial, while antibody response to proteins is directed to both bacterial and virus. So we suggest a modification to be introduced: Proposed change (if any): Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure (PSAF)* or serum IgG level of <4 g/l. PSAF= failure to mount at least a 2-fold rise in IgG antibody titre to pneumococcal polysaccharide and/or polypeptide antigen vaccine.	
	Severe infections are the first cause of death after solid organ transplantation. Secondary antibody deficiency after solid organ transplantation has been demonstrated to be a risk factor of severe bacterial, CMV and fungal infections. IgG hypogammaglobulinemia is a risk factor of severe bacterial infections in heart, lung, kidney, liver and intestine transplantation despite antimicrobial prophylaxis.	Acknowledged

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	Intervention studies have demonstrated the role of IgG reconstitution by use of IVIG in the following settings: Prevention of infection in heart recipients with IgG hypogammaglobulinemia. Secondary prevention of infection in heart recipients who develop severe infections a who have IgG hypogammaglobulinemia at the time of infection. Sarmiento E, et al. Int Immunopharmacol. 2005; 5(1):97-101;Sarmiento E, et al. Transpl Infect Dis. 2016; 18(6):832-843;Yamani MH,et al. Transpl Infect Dis. 2001;3 Suppl 2:40-3.37; Yamani MH et al. J Heart Lung Transplant. 2005 Nov;24(11):1766-9; Carbone J et al. Clin Transplant. 2012; 26(3):E277-83; Carbone J et al. Transplant Proc. 2007 Sep;39(7):2385-8.	
9	Comment: The inclusion of CIDP and MMN as "established indications" should be made for all preparations of human normal immunoglobulin with a similar pharmacokinetic (PK) profile to IVIg. Shire supports the addition of CIDP and MMN to the list of “established indications" for IVIg. Furthermore, Shire proposes that consideration be given to extending the "established indications" to Ig products with similar pharmacokinetics to IVIg - such as facilitated subcutaneous immunoglobulin (fSCIg). Facilitated SCIg presents a unique paradigm in that because its PK behaviour resembles IVIg more so than SCIg, it is more suited to inclusion in the Notes for Guidance on the Clinical Investigation of Human Normal Immunoglobulin for Intravenous Administration (IVIg) (EMA/CHMP/BPWP/94033/2007 Rev. 3) and the Core SmPC for Human Normal Immunoglobulin for Intravenous Administration (IVIg) (CHMP/BPWP/94038/2007 Rev.5) rather than the corresponding SCIg guidance.	The line of argumentation is appreciated and as pointed out by Shire there is some scientific discussion about the necessity of high dose IVIG peaks in the initial treatment of CIDP and MMN– however this data has not yet fully matured. So whether SCIG can fulfill the same efficacy expectations both in initialization and in maintenance has not been fully elucidated and may require further clinical data.

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	Facilitated SCIg preparations can provide comparable bioavailability and systemic exposure to IgG relative to IVIg preparations and thus meet the requirements for bioequivalence to IVIg (Wasserman, 2012). These pharmacokinetic aspects of fSCIg result in administration parameters that more closely mirror an IVIg infusion rather than a SCIg infusion. The frequency of infusions is the same as that for IVIg treatment (once every 3 to 4 weeks), the volumes and rates of infusions are virtually identical to those administered IV (up to 600 mL/site and 300 mL/hour), and the number of infusion sites does not exceed that required for IVIg. Consequently, fSCIg administration provides the same systemic exposure to IgG as IV administration and can be expected to provide the same therapeutic efficacy as IVIg in autoimmune neurologic diseases. At the same time, fSCIg offers many of the advantages inherent to SCIg therapy such as a superior systemic adverse event profile, increased convenience and improved health-related quality of life. The exact mechanism of action of high dose IgG in neurological conditions has not been fully elucidated and the importance of the various pharmacokinetic parameters to this effect is not well understood. As there are no defined relationships between specific IgG PK parameters and clinical response that can be used to guide treatment in CIDP and MMN (Van Doorn, 2011; Rajabally, 2013; Kuitwaard, 2013; Vlam, 2014), optimum dosing regimens in clinical practice tend to be empirically determined, and individualised therapy is aimed at reducing dose and optimising frequency to the minimum effective level (Rajabally, 2006; Lucas, 2010; EFNS, 2008). Clinical experience suggests that considerably lower doses of IVIg than the	

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	recommended initial dose of 2 g/kg may be effective (Rajabally, 2006) and that trough levels of serum IgG (Lucas, 2010; Markvardsen, 2013) as well as the attainment of stable serum IgG levels (Kuitwaard, 2013; Markvardsen, 2014) may be important predictors of clinical outcome. Furthermore, SCIg – which is characterised by a flatter serum IgG concentration profile compared to IVIg - has been used successfully in CIDP and MMN (Berger, 2014; Rajabally, 2014). Taken together, these data suggest that the high serum IgG peaks associated with IVIg therapy of CIDP and MMN may not be crucial to clinical response. The above information in addition to the infusion parameters of facilitated SCIg collectively support similarity to IVIg treatment and extending the label should consequently be considered for fSCIg. Facilitated SCIg thus offers a number of advantages in CIDP and MMN patients by virtue of its PK attributes. To-date, CIDP (Köller, 2006; Lee, 2008; Cocito, 2011; Markvardsen, 2013 & 2014; Cocito, 2014) and MMN (Harbo, 2009; Eftimov, 2009; Harbo, 2010; Dacci, 2010; Misbah, 2011; Cocito, 2014) patients who were successfully switched from IVIg to SCIg have been administered the equivalent monthly IVIg dose in divided weekly doses – an obligatory dosing regimen for conventional SCIg preparations (16 to 20% IgG) because of the limited volume of fluid that can be tolerated by SC administration and the lower bioavailability of SCIg preparations, estimated as ~70% based on a meta-analysis of data from over 1000 PID patients (Berger, 2013). These dosing limitations are illustrated by reports of SCIg use in CIDP and MMN, where weekly maintenance doses of IgG ranged from 5 to 50 g/week, with maximum initial doses per site of 3.2 g (20 mL) administered at a rate of 20 mL/h. In the 2 year follow-up study in MMN reported by Harbo et al (Harbo, 2010), patients received 4 to	

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	16 infusions per week at a rate of 20 mL/site to administer 80 to 320 mL (12.8 to 51.2 g) of 16% IgG using up to 3 pumps simultaneously. This is in stark contrast to fSCIg which would typically require one infusion per month and emphasises the advantages of fSCIg therapy, which can overcome the dosing constraints of conventional SCIg therapy for neurological indications. Furthermore, in comparison to IVIg therapy, fSCIg offers the benefit of (a) improved tolerability and a superior systemic safety profile, including fewer serious haemolytic, thromboembolic and hypersensitivity reactions, (b) an alternative for patients with poor venous access, (c) the option for self-infusion/home treatment, (d) increased convenience and dosing flexibility, and (e) an overall improvement in the patient's health-related quality of life. Proposed change (if any): Include CIDP and MMN as “established indications” for all routes of IgG administration that provide similar pharmacokinetics to IVIg.	
	Shire welcomes the EMA's proposal to expand the "established indications" for IVIg to include the immunomodulatory indications of CIDP and MMN. This recommendation takes into consideration: • The significant body of evidence establishing the safety and efficacy of IVIg in CIDP and MMN, including data from randomised controlled trials (RCTs) in CIDP (Eftimov, 2013 [meta-analysis of 8 RCTs]) and MMN (van Schaik, 2005 [meta-analysis of 4 RCTs]; Harbo, 2009; Hahn, 2013). • Consensus guidelines from the Joint Task Force of the European Federation of Neurological Societies (EFNS) and the Peripheral Nerve Society (PNS), which recommend IVIg (level A recommendation) as a first-line treatment for CIDP (EFNS/PNS,	

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	2010a) and MMN (EFNS/PNS, 2010b). • Consensus statement of the use of IVIg in the treatment of neuromuscular conditions from the American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) (Donofrio, 2009). • National (EU) guidelines for IVIg use, which propose evidence-based IVIg use in specific neurological indications (BfArM, 2009; DH, 2011; NHS Scotland, 2011). • The centralised and national approval of selected IVIgs for treatment of CIDP and MMN (as summarized in EMA/CHMP/BPWP/572805/2013). • The extensive evidence-based use of IVIg for CIDP and MMN attesting to the "established" nature of this treatment option. For instance, neurological indications are the single largest user of IVIg in England, accounting for more than 40% (by volume) of the total IVIg usage and 25% of IVIg recipients; CIDP and MMN represent almost 75% of the IVIg volume prescribed for neurology (DH, 2010) • Accessibility to an increased number of approved IVIg products, thus permitting patient needs to be matched to IVIgs with specific product attributes – e.g., in terms of sodium and sugar content, volume load and tolerable infusion rates – characteristics which can differ considerably among different IVIg formulations (Gelfand, 2006; Chérin, 2010) • The need for rational utilisation of IVIg, a human plasma-derived product. Availability of a greater number of IVIg products approved for use in two major indications is expected to reduce the likelihood of shortages. • Ethical, economic and practical consequences of conducting further clinical studies for regulatory approval in CIDP and MMN –	

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	orphan indications where the benefit-risk of IVIg is clearly established: The enrolment of treatment-naïve patients in interventional clinical trials is demanding because of (a) the low prevalence of CIDP and MMN, and (b) the ethical implications of exposing symptomatic patients to progressive neuronal damage when effective treatments exist. • Similarly, the participation of treatment-experienced patients also presents ethical constraints as patients are required to interrupt treatment until clinically significant disease deterioration. • The cost-burden of mandatory confirmatory clinical trials with IVIg is ultimately transmitted to the health care system and diverts resources from other areas of needed research. In conclusion, Shire believes that the available data are adequate and provide evidence for a class effect of IVIgs and support the inclusion of CIDP and MMN as "established indications" in the Core SmPC.	
	Shire welcomes the EMA's proposal to review the requirements for use of IVIG in the case of secondary immunodeficiency (SID). This recommendation takes into consideration: • Secondary hypogammaglobulinemia may be the result of conditions and therapies over and above CLL and MM; such as other B cell malignancies, transplantation and iatrogenic causes (e.g., rituximab), • There is a significant body of evidence establishing the safety and efficacy of IVIg in preventing infections in patients with secondary immune deficiency (Cooperative Group for the Study of Immunoglobulin in Chronic Lymphocytic Leukemia, 1988; Chapel, 1994; Sklenar, 1993; Griffiths, 1989; Boughton, 1995; Molica, 1996; Makatsori, 2014; Roberts, 2015). • These authors studied IgRT after severe infection in patients	Expansion of SID indication for SCIGs is yet to be discussed

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	with SID from various causes • There is support in various guidelines (Ludwig, 2007; Smith, 2005; Snowden, 2011; Anderson, 2015; Kyle, 2008; Perez, 2016). • There is significant evidence of an association between infection risk and poor functional antibody responses in patients with SID analogous to patients with PID (Robertson, 2000; Makatsori, 2014; Karlsson, 2011; Parry, 2015). In conclusion, Shire believes that the available data are adequate and provide evidence for the revision of the indications for use in secondary immunodeficiency in the Core SmPC, and that the data as outlined above also demonstrates that subcutaneous Ig should be included/considered for a similar expansion in the indication for SID in the core SmPC for subcutaneous Ig products.	
10	Could I please ask that you strongly consider adding in requirements for the investigation of the safety and efficacy IVIg products in children for **all indications** prior to marketing authorisation. So that IVIg products are produced that we know are safe and effective in this vulnerable patient population. Paediatric IVIg recipients frequently have adverse reactions to IVIg, please see recent article by Berg et al. It is not appropriate to allow registration for products based on studies performed in adults and extrapolating to children. For example Kawasaki disease is a condition unique to children that is treated with doses of IVIg that is generally far higher than received by adults (2g/kg versus 1g/kg). 1) Products for which an application for a marketing authorisation is to be submitted, referred to as “new products” in the text	We agree that data in children is beneficial. For the past 60 years IVIG, SCIG, and IMIG have been routinely given to children for a wide variety of disorders with good efficacy and safety results. All marketed IVIGs and SCIGs are studied in a subset of PID children who are in the trial for one year. In a Worksharing exercise completed in 2010 encompassing IVIGs, SCIGs or IMIGs, 8 different MAHs submitted **41 studies** all of which included paediatric patients. This was in accordance with Article 45 of the Regulation (EC) No 1901/2006. The submitted studies showed heterogeneity in design, quality, indication, age of pediatric population and in the time period they were performed. However, the PK, efficacy and safety results did not reveal major differences between adults and children suffering from the same disorder. No changes in the core SPC or the product specific

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	Immunodeficiency syndromes - 40 patients with primary immunodeficiency syndromes (PID), whereby 20 of these should be children or adolescents with an age distribution representative of this patient population. **(It is good to see that children are included in this section, however this is often low dose IVIg therapy)** ITP - 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. Standard doses should be studied (0.8 - 1 g/kg on day one, which may be repeated once within 3 days, or 0.4 g/kg/day for 2-5 days).**(No requirement to study a new IVIg product in children)** Kawasaki Disease - In the absence of specific clinical trial data in these indications, the efficacy in primary immunodeficiency syndromes and in ITP should be established. The dosage regimen should be justified in the expert report. If other dosage regimens are requested, they should be supported by clinical data. **(No requirement to study a new IVIg product in childrenat doses of 2g/kg as used in Kawasaki disease)** 2. Change in the manufacturing process of authorised products. - If a significant impact on the activity of the immunoglobulin cannot be excluded, data on pharmacokinetics and safety in PID patients is required. In addition, since the biological rationale for efficacy in ITP is not completely elucidated, efficacy and safety in ITP patients should also be provided with the application. - **(No requirement to study a modified IVIg product in**	SmPCs/PILs were considered necessary. We endeavour as a group to liaise with the Paediatric Committee and align our approach as best possible. Since 1995 the BPWP (after evaluating **pivotal studies** in each indication) has taken the pragmatic approach of extrapolation both for adults and for children. The extrapolation exercise is: a) From PID adults and children to SID adults and children b) From ITP adults to all age groups of ITP, GBS, Kawasaki

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	children – when the modified product could include a different stabilising agent such as fructose which can have massive implications to a neonate or young child treated with this product) I kindly request you review your guideline as your guideline is having flow on effects to other governing agencies and to pharmaceutical companies, by not necessitating them to study their product in children. Products are being licensed for use in adults and then paediatricians are forced to use medications and drugs off-label. Drug companies will not perform trials in children unless it is a necessity for marketing, they will say that if paediatricians choose to use it, it is off label.	
11	1. Introduction The current Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg) dated 22 July 2010 (EMA/CHMP/BPWP/94033/2007 rev. 2, hereinafter "the Guideline") states that several references from the literature show a positive effect of IVIg for the treatment of CIDP and MMN. The EMEA/CHMP/BPWP/361857/2006 Report of EMEA expert meeting on the revision of the core SPC and note for guidance for IVI**g** 5-6 July 2006 states that "*IVIgs are currently used off-label (especially in neuro-immunological disorders)*". To facilitate the registration of IVIg preparations in these indications and limit off-label use, the BPWP proposed in its 2010 revision of the Guideline to alleviate the clinical development requirements by asking pharmaceutical companies to provide "confirmatory data" with the product to be registered in addition to data from the literature, and no longer to conduct a pivotal clinical trial. The new revisions of the Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg)	The BPWP endeavours to keep the GLs and coreSPCs up-to-date with the current evidence. The precedent of extrapolation was initiated with the introduction of the initial GL and coreSPC in 1995; (rapporteur FR) where a PID study and an ITP study were sufficient to claim the indications CLL, MM, Kawasaki and BMT. GBS was later added to the SPC (on the base of 3 RCT with different IVIGs) and no more studies were required

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	(EMA/CHMP/BPWP/94033/2007 rev. 3) and the Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg) (EMA/CHMP/BPWP/94038/2007 Rev.5), hereinafter referenced as “the new revisions of the guidelines”, released for public consultation propose that CIDP and MMN be considered as “established indications” such that specific studies are no longer needed to be performed for these two indications as long as the IVIg have allegedly been shown to be effective and safe in the model indication. LFB does not understand the underlying justifications (or benefits expected) of such a significant evolution from the 2010 consensus against the integration of MMN and CIDP in the IVIg Core SmPC, to their integration today: - Is it to improve access to IVIg for patients? There is no urgent need to introduce these indications in Europe; Off-label use in these two indications is not the case as some IVIg preparations are granted one of these indications in <u>all</u> EU countries and, in addition, no shortage in supply has been deplored for years. Therefore access to patients appears not to be an issue. - Is it to improve innovation in the field? The efforts in innovation would probably not be transferred to new indications as companies will no longer wish to invest in clinical research for new indications if after a short while, these indications are being granted to all, not allowing for a proper return on investment for those who make the efforts to finance the appropriate trials. On the contrary, requiring clinical trials to get approved is the best way to accumulate	

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	well designed trials and data, and thus improve knowledge and innovation. - Is it to converge with a global regulatory move in this sense? However, there is no consensus worldwide on such a regulatory pathway of progressively integrating indications without supportive related clinical data, in particular with FDA. - Is it for the benefit of plasma fractionators? We will show in our comments that it could be the opposite. In this context, LFB considers that the part of the update of the guidelines related to these two indications, as proposed, would raise major issues relating not only to the conformance to EU legal rules, but also to (i) an incomplete medical justification to stop requiring clinical trials in CIDP and MMN; (ii) a negative economic impact in EU and on innovation that could potentially impair, in the long run, the patient access to IVIgs. For these reasons, LFB considers that the current guidelines should not be amended regarding MMN & CIDP and the BPWP should therefore respond to all these arguments.	
11	**Reasons why the corresponding revisions of the guidelines are not justified from a medical perspective** In 2010, the BPWP insisted on the scientific questions requiring answers before agreeing on the efficacy and treatment schedules of IVIg for CDIP and MMN, thus justifying the need for a clinical trial. Answers from BPWP to comments on draft clinical guideline IVIg, as stated in the BPWP answers to comments received on the guideline (IVIg) (EMA/CHMP/BPWP/94033/2007, rev. 2 said: *"Due to a number of shortcomings in the clinical trials in*	The ICE trial (Gamunex) answered a number of these questions and confirmed the results gained hitherto.

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	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. *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."* In this light, the corresponding new revision of the guidelines pose key questions which LFB would like to address, related to: • The notion of 'similarity' and "interchangeability" between the different IVIgs, without denying a class effect; • The extent of clinical data needed before an indication can be considered as "established" for IVIgs and allows inclusion of this indication in the Core SmPC; • The extent of data collected, since 2010 that allowed BPWP to change its mind about the efficacy of all IVIGs in these indications; • The extent of data collected since 2010 that allowed PBWP to extrapolate the possible efficacy of one product to another;	LFB wrote in their comments to the Concept Paper: "<u>There is no class effect</u>"

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	• The relevance of the ITP model to validate MMN and CIDP indications; • The restriction of the access to the sole products under market approval to lower as much as possible the risk for patients. LFB wishes to underline, as it will be shown in this chapter that none of the conditions set out in 2010 to consider that an indication can be regarded as established have been met; indeed**,** to date, no published or approved head to head clinical trials have shown the equivalence of different IVIg preparations in terms of efficacy in MMN and CIDP indications. The demonstration is not given on how the new scientific and medical knowledge accumulated since then lead to the conclusion of the BPWP. Since 2010, only one clinical trial in CIDP (LFB recently finished) and one in MMN (ongoing LFB) are comparing products in these indications. **This, in itself, should lead the PBWP to consider that the Guidelines cannot yet be revised, as to do otherwise would raise serious legal questions about the coherence of its positioning created for fractionators in 2010**.	
11	**2.1. IVIgs have not being registered as biosimilar medicinal products (§4 of Article 3 of EU Directive2001/83)** IVIgs are, like most of the biological products, defined both by their active substance and their manufacturing process. However unlike most of the other plasma derived products, which are by definition a much diluted active substance in a stabilizing protein, as in the particular case of the IVIgs, the active ingredient is, by itself, a complex combination of various proteins, making each product even more different. This logically translates in the regulatory pathway	

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	used indeed so far in EU for their registration: to our best knowledge, none of the current IVIgs registered in EU have been developed through a biosimilar regulatory pathway. According to current EMA IVIg guidelines, IVIg are not considered similar biological medicinal products, as applicants are requested to perform 2 clinical trials in 2 model indications for each specific IVIg, confirming the efficacy and safety, with no comparison to a "reference product". No head to head clinical trials have shown the equivalence of different IVIg preparations in terms of efficacy in MMN and CIDP indications as well as in established indications (i.e., PID and ITP). Moreover, IVIgs cannot be considered as similar or interchangeable in terms of safety as it is well recognised by the scientific, medical and regulatory community. **2.2. LFB do not deny an IVIg class effect; but recalls that it has no legal or regulatory basis to allow a registration** Although Guidelines for the development and Core SPC are dedicated to IVIg and a class effect could be recognised, this artefactual – and not regulatory – status cannot be the foundation for a specific regulation promoting complete absence of clinical data generated	The proof-of-principle has been established since 1995 whereby PID and ITP are seen as model indications for replacement therapy and immunomodulation respectively. One head to head study showed an insignificant treatment difference of 0.004 between KIOVIG and Gammagard in CIDP https://www.ncbi.nlm.nih.gov/pubmed/20587484 We agree that some safety issues are related to a specific product (e.g. type of stabilizer, IgA content). Some other safety issues are seen with all IVIG products and are described accordingly in 4.4. and 4.8. of the coreSPC. Moreover, data is collected and assessed yearly in PSUSAs – this single safety assessment. However, the discussion here is about the similarity of efficacy. As mentioned above the extrapolation from PID and ITP to other indications has been the status quo and accepted by all stakeholders since 1995. (Rapporteur FR) In their original rebuttal LFB did deny a class effect

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	with the product to be registered in the indication, outside the general legal framework of Directive 2001/83/EC requiring clinical data to assess the product benefit/risk ratio in the indication. With respect to efficacy, although the BPWP suggests that the beneficial clinical effects of different brands are likely to be similar; a few head-to-head trials comparing IVIgs in various indications were performed and enrolled a small number of patients. In Kawasaki disease, a higher risk of IVIg non-responsiveness was shown with IVIg having a beta-propriolactonation step (*Lin, 2013 and 2014).* Some of the variability in the development and clinical manifestations of the disease, and ultimately the response to IVIG, may relate to differential antibody Fc glycosylation patterns or may be explained by genetic and functional variations in FcγR expression. Regarding safety, it is highly recognised that IVIgs are not similar due to the excipients used for their formulation and the impurity profiles related to manufacturing processes differing from one to the other leading to various level of activated factor XI (risk factor for thrombosis), anti-A and anti-B haemagglutinin (risk factor for haemolysis) in the IVIg preparations. Several recent events (thromboembolic accidents, haemolysis) are a good illustration and show the non-similarity of IVIg products in terms of Pharmaceutical quality, especially with respect to their impurity profiles. In this light, the safety data collected in pivotal clinical trials in PID and ITP patients which are treated with low doses (PID) or single course of high doses (ITP) could not be considered sufficient to avoid	In the article by Lin the product with beta-propriolactonation is Intraglobin F (Fc modified: excluded by the GL) which is not considered state of the art and is no longer authorised e.g. in Germany. The acidified product led to a higher rate of aneurysms but the severity grade was not clear; the surrogate marker for persistent aneurysms was use of anticoagulation – here acidification seemed to have a protective effect. So the data was not conclusive. As mentioned above, impurity differences are acknowledged and safety differences are recognized and addressed in the coreSPC. For Marketing Authorisation PID data is collected over one year (per patient). Further (long term) data is collected and assessed yearly in PSUSAs (single safety assessment) LFB slightly misquoted this statement, the actual text is as follows:

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	the need for generating further safety data in MMN and CIDP patients which are treated with high doses on a long-term basis. Acknowledging that there are good reasons to consider IVIgs as not similar and considering this key regulatory status, it is hard to understand how, from a strictly regulatory standpoint, it is possible to bestow identical clinical effects from one IVIg to another, which seems to be the basis of the BPWP reasoning, especially when to date, immunoglobulins are not considered as similar products nor interchangeable as it was clearly emphasised in recommendation 4 of the Kreuth III meeting ("*The WG agreed that Igs are not generic products*"… "*Immunoglobulin products differ from one another*") where the Group 2 Rapporteur was also the Guideline Rapporteur. As a product is registered with regards to its benefit/risk ratio, even a class effect with regards to efficacy would not lead to identical benefit/risk ratios between various IVIgs. ***In light of the foregoing, LFB considers that the guidelines cannot be modified and BPWP should respond in details to such arguments if it wants to justify scientifically and regulatory-wise such a revision.***	"*The (Kreuth) WG agreed that immunoglobulins are not generic products, and had extensive discussion about when they are similar and when they are different. There was agreement that the beneficial clinical effects of differing brands are likely to be similar, but that side effects may differ from product to product, and even from batch to batch*" The B/R ratio is assessed for each product and compared to other products. Given e.g. the wide margins of safety frequency assessment (by factor 10) relevant differences are only seen if there is a major occurrence such as the TEEs/haemolysis. In the last PSUSA 2017 In the completed and ongoing MAH-sponsored controlled clinical trials there have been no reports of significant lack of effect which would alter the evaluations of the integrated benefit-risk evaluation
11	**1.2. What should be the requirements to consider CIDP and MMN indications as established?** LFB believes as it has been stated by the BPWP in 2010, that it is too early to consider these indications as established as there are still important uncertainties related to the IVIg therapy in these clinical	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	settings. From the moment CIDP and MMN are considered as "established indications", it is very likely that the source of clinical trials will dry up, while there are still uncertainties on the optimal scheme of IVIg treatment (dose, interval between doses, and duration of treatment…) in these indications that need to be further documented by clinical trials. In 2010, the BPWP insisted on the scientific questions requiring answers before agreeing CIDP and MMN candidates as "established indications" and to our knowledge, these questions have not been solved since 2010. Overview of comments received on the guideline (IVIg) (EMA/CHMP/BPWP/94033/2007, rev. 2 states that: *"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 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."* *"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*	The reply to the overview of comments received is not to be confused with the GL. At the EMA workshop in 2006 the database was deemed not quite sufficient; the ICE trial enhanced the CIDP evidence database (2008) considerably. This was followed by the authorisation in 2010 in FR of Tegeline (retrospective study), in 2012 of IgVena (RCT vs prednisone), in 2013 of Privigen (open-label), in 2015 of Octagam in DE (retrospective study in FR). In 2013 the Cochrane review concluded on the larger base of data (8 RCTs, including 332 participants) that "the evidence from RCTs shows that IVIg improves disability for at least two to six weeks compared with placebo, with an NNTB of three. During this period it has similar efficacy to plasma exchange, oral prednisolone and intravenous methylprednisolone. In one large trial, the benefit of IVIg persisted for 24 and possibly 48 weeks" For MMN the database was enlarged in 2012 by a study with Kiovig and one placebo-controlled study in the US with

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	were used and the studies had other methodological issues (timing of the primary endpoint; the definition criteria for CIDP). *Five different IVIg brands were used.* *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."* *"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.*	Gammagard In view of this development over the last 7 years international guidelines (Australian GL 2012, Canadian GL 2010, UK DMP 2012, BE Recommendation 2011) have come to recognize CIDP and MMN as established indications (with class 1 evidence). Furthermore CIDP is seen as being a form of chronic GBS with both disorders lying on a neurological continuum. In 2010 one head- to head trial was performed and showed an insignificant treatment difference of 0.004 between KIOVIG and Gammagard in CIDP https://www.ncbi.nlm.nih.gov/pubmed/20587484 The duration of therapy was one aspect addressed in the ICE trial. The dosing with IVIGs in all indications will remain a matter of tailoring to the patients' needs. This is reflected in the coreSPC both for replacement and immunomodulation. The limitation of the therapy in to 6 months in CIDP follows the recommendations of e.g the

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	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." *"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)."*	Australian GL and for MMN those of Tegeline. We acknowledge that it would be nice to know the exact pathogenesis and the exact MoA of IVIGs/SCIGs in the various disorders; however, this is also not known for established indications such as ITP, Kawasaki, and GBS. It would be appreciated for all stakeholders to help devise qualification criteria (if this is possible) and for industry to cooperate on common trials
	In fact, the BPWP has not explicated nor detailed unambiguously and communicated, ever, what are the qualification criteria for an indication to become "established, as announced in 2014 in the §4 'Recommendation' of the Concept paper on 'Guideline on the clinical investigation of IVIg and Core SmPC EMA/CHMP/BPWP/572805/2013". **Moreover, CIDP and MMN and to our knowledge, these questions have not been solved since 2010.**	The Cochrane (2013 and 2016) CIDP review states about the 8 RCTs they included for review: These trials were homogeneous and the overall risk of bias low. In addition, the 8 different trials used different IVIG products and measured a variety of clinically relevant endpoints (which have evolved over time) and had positive outcomes for the patients concerned.

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	2.3.1. Reasons why CIDP should not be considered as an established indication The CIDP published clinical trials reporting the efficacy and safety of IVIg (See Annex 1: Table 1) showed heterogeneity in terms of: - sample size (from 6 to 117 patients), - study population (patients naive to IVIg treatment or treatment initiation for 9 clinical trials and treated patients or maintenance treatment for 3 clinical trials), - primary efficacy endpoint (Rankin scale for 1 study, MRC score for 1 study, average muscle score for 1 study, number of patients who stopped the treatment for 1 study, INCAT score for 2 studies, Neuropathy Disability score for 2 studies, ODSS for 2 studies), - duration of exposure to IVIg (one course for 2 studies, 2 courses for 3 studies, 4 courses for 1 study, 24 weeks for 3 studies) , - IVIg dose regimen. The current guidelines of the European Federation of Neurological Societies (EFNS) in the diagnosis and treatment management of CIDP (2010) states: *"For induction of treatment: IVIg (level A recommendation) or corticosteroids (level C recommendation) should be considered in sensory and motor CIDP in the presence of disabling symptoms…The **usual first dose** of IVIg is 2.0 g/kg over 2-5 days.* *For maintenance treatment: If the first-line treatment is effective, continuation should be considered until the maximum benefit has been achieved and then the dose*	EFNS recommends IVIG (not a particular brand) Same as coreSPC proposal Same as coreSPC proposal We agree that short and long-term management has to be individualized.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	*reduced to find the lowest effective maintenance dose…**No evidence-based guideline can be given as none of the trials systematically assessed long-term management.** IVIg given in doses of 1.0 g/kg over 1-2 days every 3 weeks has been shown to be efficacious over 24 weeks…**but the appropriate dose needs to be individualized (usually 0.4-1.2 g/kg every 2-6 weeks)**"*	It is not unusual that in routine practice, therapeutic schemes vary between EU states – this will depend on many factors, not least their health system and their budget. E.g. also with a coreSPC for Hep BIG and Anti-D Ig – the doses also vary from country to country. PID and SID also have ranges of doses.
	The EFNS does not recommend a specific IVIg scheme (posology, number of course, interval between courses) for the induction of treatment and for maintenance treatment because there is not an accumulative body of evidence from published clinical trials in order to define an IVIg appropriate scheme: - The same scheme was similar in only 2 clinical trials (Hughes RA, 2008 and Leger JM, 2013): 2 g/kg for the first course then 1g/kg/course every 3 weeks - In another recent clinical trial, the dosage of IVIg was 2 g/kg every 4 weeks during 6 months (Nobile-Orazio 2012) - For older clinical studies, the scheme was 2 g/kg and sometimes continued by some courses at 2 g/kg every 2-3 weeks.	In a recent article a 2 year retrospective follow-up looked at 21 CIDP pts receiving 1 g/kg every 3-6 weeks and could confirm efficacy of IVIg as first line therapy in CIDP. "Doses and frequency of IVIg application should be adapted based on clinical evaluation and analysis of long-term electrophysiological findings " https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5367649/
	In routine practices, therapeutic scheme varies according to the European members States. For example, in France, patients with CIDP are used to receive the first 3-6 IVIg courses at 2 g/kg/month, and then if the neurological status is stable, French neurologists increase the interval between consecutive courses (4 to 8 weeks) and in a second time, decrease the IVIg dosage.	The development of neurological disability scores is up to the experts in these fields and as mentioned above a variety of these have been incorporated either as primary or/and secondary endpoints in the 8 RCT reviewed in Cochrane

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	Despite results of published clinical studies and recommendations of the EFNS, there is no evidence-based consensus on dose regimen schedule of IVIg. This is particularly disturbing since the therapeutic regimen has an impact on the efficacy (improvement in neurological status, prevention of the occurrence of axonal loss ...). For example, in a clinical study of 11 patients long-term IVIg maintenance therapy (≥ 1 year) was shown to improve neurophysiological parameters, possibly by reducing the immune response and thereby fostering nerve re-myelinisation (Vucic, 2007). In another publication, 4 CIDP patients resistant to corticosteroids and plasma exchange and responders to IVIg with an efficacy window <15 days were reported to progressively improve their disability scores over a mean periods of 10 months after a high dose (mean monthly dose of 3 g/kg) and fractionated IVIg therapy (Debs, 2016). In addition to IVIg regimen schedule, further investigations are still needed and required to continue clinical research with IVIg. As of now, the adjusted INCAT disability score is considered as the most relevant marker of treatment response in patients with CIDP. However, other methods need to be further evaluated in clinical trials. In the ICE study, the grip strength measurement (Martin Vigorimeter) indicated significant improvement (>8 kPa) sooner than the INCAT disability scale in patient receiving IVIg compared with placebo, as early as day 16 after treatment. Quality of life scales have also to be examined after IVIg treatment using relevant scoring system and correlated with the INCAT disability scale. Serum IgG level is a marker for which a significant correlation has been identified between the mean rise 2 weeks post-infusion and the interval between infusions (the higher the IgG level at 2 weeks, the greater the time between infusions) (Rajabally, 2013). Further	The quality of evidence in the CIDP Cochrane Review for “Significant improvement in disability scale used in original study” was considered high (definition of high: “Further research is very unlikely to change our confidence in the estimate of effect”). The RR compared to placebo was 2.4 in 269 pts. Monitoring of biomarkers is appreciated See above for studies since 2010. As mentioned above this is quoted from the Overview of

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	investigation is warranted to confirm its predictive value of treatment need. In the ongoing LFB clinical studies in patients with CIDP, multiple exploratory studies monitoring biomarkers before and after IVIg administration have been planned to investigate potential predictive markers of response: anti-contactin1 (CNTN1) and anti-neurofascin 155 (NF155) antibodies titres, FcγRIIB expression on B cells, B cell activating factor (BAFF), complement components (C3 and C4 antigens, CH50), and serum total IgG trough levels at each visit. In conclusion, further clinical trials are needed to determine the maintenance dose of IVIg, interval between doses, and duration of treatment. Further research is also needed to identify predictors of response, long-term benefits, safety and cost-effectiveness and to validate new promising neurologic scales. These elements would allow more accurate recommendation to be inserted in the SmPC to the attention of prescribing physicians. **For CIDP, since the current guideline (2010),** only 5 new studies with only one randomised, placebo controlled, the four other observational, **represent an insufficient knowledge improvement to change the BPWP policy as "***data on dosing, duration of therapy, subgroups that respond and possibly the underlying mechanisms of IVIg in the individual pathologies* "has not been *collected*. Therefore they cannot motivate a change of position from the BPWP since the last assessment in 2010. **2.3.2. Reasons why MMN should not be considered as an established indication** The MMN published clinical trials reporting the efficacy and safety of	Comments and did not find its way into the GL as e.g. MoA would be difficult to address in an MAA. IVIGs have proven effective in a number of indications but the MoA has not been elucidated (e.g. ITP, GBS, Kawasaki) –this did not hinder a MA or for these indication to become established. See again the GL mentioned above (Australian, Canadian, UK DMP and BE recommendation) and EFNS (no specific brands are mentioned) Apart from the recommendations of international GLs one should also keep in mind that *MMN is unresponsive to steroids and in about 20% of cases may even deteriorate with this treatment. Plasma exchanges are also ineffective or detrimental, having caused in some reported cases severe clinical worsening and an increased number of Conduction blocks.* http://pmj.bmj.com/content/84/992/287.full As mentioned also for CIDP the doses will have to be tailored to the individual patients' needs and the doses in the coreSPC are given only as guidance (hence the scope

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	IVIg of which 40% were observational (See Annex 2: Table 2) showed also heterogeneity in terms of: - number of analysed patients (from 6 to 88) - study population patients (naïve to IVIg treatment or treatment initiation for 3 clinical trials and treated patients or maintenance treatment for 4 clinical trials), - primary efficacy endpoint (MRC score for 4 studies, Neuropathy Disability score (NDS) for 1 study, GNDS for 1 study) - duration of exposure to IVIG (one course for 1 study, 2 courses for 1 study, 12 weeks for 2 studies, 6 years follow-up for 1 study) - IVIg regimen The EFNS guidelines (*Joint Task Force of the EFNS and the PNS, 2010*) mentioned that *"**IVIg (2 g/kg given over 2–5 days)** should be the first line treatment (level A) when disability is sufficiently severe to warrant treatment. If an initial treatment with IVIg is effective, repeated IVIg treatment should be considered in selected patients (level C). The frequency of IVIg maintenance therapy should be guided by the response. Typical treatment regimens are **1 g/kg every 2–4 weeks or 2 g/kg every 1–2 months**."* In published clinical trials, the IVIg regimen was very heterogeneous: 2 g/kg every 8 weeks for 1 study, 2 g/kg/month for 1 study, 0.4 to 2 g/kg/every 2-4 weeks for 1 study. Although the initial treatment with IVIg is well defined and recommended by consensus guidelines, maintenance therapy	given in the coreSPC) In addition, one further placebo controlled study was performed with Gammagard in the US in 44 patients (23% difference in grip strength; 36% deterioration in placebo vs 12% in verum) thereby confirming the data collected so far. http://onlinelibrary.wiley.com/doi/10.1111/jns5.12046/abstract See comments above

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	requires further clinical studies. Comparative dosing studies with long-term follow-up are needed to establish the dose and treatment interval preventing axonal degeneration which could lead to worsening of the disability. In addition, predictive markers for response other than clinical criteria (patient's initial response or interval between the first dose and decline in muscle strength) should be investigated to assess their correlation with long-term response and help decision on maintenance treatment. In the LFB clinical studies in patients with MMN, two exploratory endpoints monitoring biomarkers before and after IVIg administration have been planned to investigate potential predictive markers of response: IgM anti-GM1 and GM2 antibody and serum total IgG trough levels. **For MMN, there is only 1 new open label study since the current guideline (2010), which represents an insufficient knowledge improvement and cannot motivate a change of position from the BPWP since the "Guideline".** **To conclude, for CIDP and MMN, the European scientific community reached a consensus for the first IVIg course, based on data from published clinical trials. However, for the subsequent courses, no consensus has been established for appropriate scheme preventing from the risk of irreversible axonal loss, and warrant further clinical investigations. Thus, there is no sufficient new knowledge for both indications since the « Guideline » in 2010 to conclude that these**	In line with medical development, GLs evolve and the endeavour to stay abreast with this development - this is one of the tasks of the BPWP. We view the current evidence as sufficient. In addition the evidence collected in CIDP and MMN constitute a larger database with many different IVIG brands than was the case for the inclusion in the coreSPC of GBS, Kawasaki, CLL, MM.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	indications are 'established' versus a target which has not been defined beforehand and that could lead to a change on BPWP position towards a revision of the Guidelines. Of note, the generation of clinical trials in MMN and CIDP in order to better document the remaining unknowns and the most efficient practices for the treatment of patients with IVIgs in these clinical settings is fully ethical, all the more as these trials are not done against placebo. ***In light of the foregoing, LFB considers that the guidelines cannot be modified and BPWP should respond in details to such arguments if it wants to justify scientifically such a revision.***	
11	**2.4. ITP is not a relevant model to extrapolate the efficacy and safety in CIDP and MMN indications** 2.4.1. Different mechanisms of action of IVIgs Mechanisms of action (MOA) of IVIg are multiple and entangled in auto-immune and inflammatory diseases. However, for each disorder, there appears to be a predominant mechanism dictated by the underlying cause (Dalakas, 2014). MOAs involved in ITP are unlikely to have the same importance as those in MMN and CIDP. In general, IVIg targets various cells (such as dendritic cells, macrophages, monocytes, B and T cells) and soluble compartments (cytokines, complements, auto-antibodies, and auto-antigens) of the immune system that are involved in the pathogenesis of autoimmune diseases. These mechanisms are non-exclusive and work synergistically to provide their therapeutic effects, which is	We agree that the MoAs of IVIGs form a highly complex matrix and these products are then infused into even more complex immune systems of patients. Some MoAs (e.g. anti-idiotype binding, FcRn saturation, complement scavenging etc.) may overlap in different AI disorders. The resulting combinatorial effects are immense. In 1995 the BPWP adapted a pragmatic approach of "proof-of-principle". If an IVIG is shown to be beneficial to the expected degree and within the expected timeframe in ITP, then certain immunomodulatory aspects were considered to be shown. A modification to the IVIG product (e.g. with beta- propriolactonation) is visible in a highly diminished response rate. The extrapolation from ITP has been accepted for Kawaski and GBS (the latter as mentioned above lies on a continuum to CIDP) by the industry – even though the MoAs are presumably not the same as in ITP.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	essentially neutralization of the activated complement, inactivation of pro-inflammatory cytokines, down regulation of Fc receptors, adhesion to molecules on macrophage, and modulation of B-cells. In CIDP patients, the inhibitory FcγIIB expression is low in naïve B cells and does not increase as B cells mature to memory cells, as normally happened in controls. IVIgs up-regulate the FcγIIB expression in correlation with clinical response (Nimmerjahn, 2011). In addition, number of circulating CD4+CD25+T- regulatory cells was shown to be reduced in CIDP patients. Increased frequency of genotype GA13-16 of the SH2D2A gene encoding for a T-cell-specific adapter protein in CIDP patients may result in a defective control and elimination of autoreactive T cells. IVIg treatment has been shown to increase numbers and function of peripheral CD4+CD25+T-regulatory cells in a mouse model (van Schaik, 2008). Regarding MMN, there is evidence that the IgM anti-GM1 antibodies, present in more than 50% of the patients, induce a complement-mediated injury at the node of Ranvier resulting in conduction block of motor nerves and muscle weakness. The beneficial effect of IVIg may be in part due to a reduced antibody-mediated complement deposition in the peripheral nerves (Dalakas 2014). MOAs of IVIg in ITP have been investigated for more than 30 years. Main mechanisms are well established and differed substantially from those reported in CIDP and MMN. The most widely accepted are the inhibition of FcγR-mediated platelet destruction and the acceleration of anti-platelet antibody elimination (Jin F and JP Balthazar, 2005). The former mechanism results from the competitive binding of dimeric or polymeric IgG (either contained in the preparation or	This pragmatic approach has (over the decades) saved industry from performing redundant studies in GBS, Kawasaki, (and for replacement) in CLL, MM, congenital AIDs etc. What is the pathogenetic mechanism in the other 50% of MMN patients? Dalakas 2014: Evidence from controlled clinical trials has established IVIg as a first-line therapy for Guillain–Barré syndrome, chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	formed just after administration) or IgG-opsonized red blood cells to FcγR, thereby sparing opsonized platelets from FcγR-mediated phagocytosis. IVIg effects on antibody elimination have been convincingly linked to the saturation of FcRn increasing the catabolism of anti-platelet autoantibodies. **To conclude, for CIDP and MMN indications, although ITP may be the unique available model so far, it is not an enough relevant one, sufficient for a registration of an IVIg without clinical confirmation in these indications.** **Thus first of all to extrapolate efficacy and safety data to chronic auto-immune diseases such CIDP and MMN patients a suitable model should be defined in terms of medical practices and mechanism of actions. In fact, in its 2017 annual staff meeting with the Fractionator Associations, EMA stated that "*Later on BPWP will reassess the physiological logic of ITP as a model*." The BPWP itself recognises that ITP as a relevant model for chronic autoimmune diseases such as CIDP and MMN with long term treatment is questionable**. In contrast to ITP as a model for chronic autoimmune disorders, the PID model indication can far better apply to all types of Primary with impaired antibody production or Secondary Immunodeficiencies with predominant antibody deficiencies requiring Ig replacement therapy and prevention of a common risk of serious bacterial infections**.** **Thus, with regard this model issue, the MMN and CIDP are a very specific case.** 2.4.2. Different medical practices not allowing Extrapolations based on clinical data from ITP How could the ITP model allow extrapolation of safety and efficacy	Long-term data on safety and efficacy of IVIGs has been collected over the past 40 years. In their entirety CIDP and MMN data cover approx. a time period from the early nineties until today. For those products who have CIDP/MMN on their label (earliest 2008) no loss of efficacy has been reported for the yearly PSUSAs. PSUSAs will continue to be performed for all products and all indications. The alternative from the pragmatic approach of the coreSPC of "proof-of-principle" via (PID + ITP) modelling, would be to eliminate it and retrospectively remove any indications from the product specific SPCs that do not have product-specific studies to support them. This, however, may endanger patient supply. Although PID is seen as a model for replacement therapy, it should be noted that PID encompasses numerous conditions that in addition to their immunodeficiency have autoimmune disorders, so that it has been recognized that IVIGs not only function as replacement but have immunomodulatory effects in PID as well.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	data from an ITP clinical study to chronic autoimmune diseases such as CIDP and MMN? Currently, for obtaining a Marketing Authorization for all indications of the Core SmPC, the Applicant must demonstrate efficacy and safety of an IVIg in 2 clinical trials: - one in Primary Immunodeficiency (PID), the model for immune-substitution, allows extrapolation for multiple myeloma, chronic lymphocytic leukaemia and bone marrow allograft, for which a similar schedule regimen of 0.4 g/kg/3-4 weeks adjusted to IgG level is recommended, - the second in “acute phase” of chronic ITP, the model for immune-modulation is likely to be extrapolated to acute diseases such as Guillain-Barré syndrome (GBS) and Kawasaki disease (KS), treated with a single course of IVIg at 2 g/kg. Whether the efficacy and safety data from the clinical trial performed in ITP can be extrapolated to chronic auto-immune diseases such as CIDP and MMN is questionable: - A different number of IVIg courses: for ITP, a single course of IVIg is recommended to raise the platelet count and prevent serious haemorrhages. By contrast, only 15 to 30% of CIDP patients required one IVIg course to observe an improvement of their neurologic impairment (*EFNS guidelines 2010*) and the majority of patients need at least 6 courses. For MMN, approximately 70% of patients need long-term IVIg infusions” (*Joint Task Force of the EFNS and the PNS, 2010*), - A different dose regimen: for ITP, there is a consensus on the dose of 1 to 2 g/kg. For CIDP and MMN, the consensus of the scientific community applies only to the first IVIg course (see	See comments above

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	above). No consensus on the dose and the interval between doses has been found for the subsequent courses, - A difference in treatment exposure to the drug: even if IVIg do not induce cumulative toxicity, MMN and CIDP patients who receive repeated IVIg courses with high doses (up to 2g/kg) have an increased risk to develop adverse events and especially serious adverse events such thrombosis and haemolysis (FDA workshops on Thromboembolic events and Haemolysis). **In conclusion, LFB would appreciate that the BPWP provides its new (since 2010) scientific arguments answering all the objections made above and supporting the use of ITP as a convincing and reliable model for MMN and CIDP, as such a robust rationale is mandatory if it wants to suppress the currently required trials to get approved in CIDP and MMN.**	
11	**3. The new revision of the guidelines will have a negative impact on innovation and potentially in the long run to patient access to IVIg** According to the concept paper on "*Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg) and Core SmPC*" published on August 1st, 2014, the foreseen impacts from the new revised guideline are: *- «...By adding CIDP and MMN to the established indications,* ***manufacturers could perform studies in other areas where the benefit has not yet been so soundly established****."* *- "...By spreading the treatment (i.e. "CIDP and MMN therapeutic indications") more evenly between available products,* ***shortages***	See below

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	are less likely to occur."	
11	**3.1. The new proposed revision of the Guidelines do not encourage manufacturers to invest and develop new indications** The BPWP policy of the guideline foresees a positive impact on innovation, and argues without demonstration that the development effort could be devoted to the development of indications for which the level of proof has not yet been established (given the fact that CIDP and MMN would be already considered as "established indications"). On the contrary, LFB identified that this proposal would probably negatively impact innovation in Europe in this field: - **End of IVIg clinical trials in MMN and CIDP in Europe:** First of all the measures in the new revisions of the guidelines will probably be deleterious on the pursuit of clinical trials in indications considered to be established for all IVIg products as, once the indication has been adopted in the core SmPC, pharmaceutical companies will no longer conduct new studies even though there are several remaining questions to be answered in these established indications (Ig dose for loading dose, maintenance dose; optimal infusion frequency; treatment duration...). Secondly, once a new indication is granted to one or few companies, the other companies may no longer be inclined to pursue in EU development in that indication as their efforts could just result in the inclusion of this said indication in the list of established indications, for all IVIg products, which	Approx. 33% of IVIG is still off-label. The plasma industry is encouraged to perform studies together in larger or orphan indications (e.g. as has been done for HIV: HIV Medicines Research Industry Forum which includes Bristol-Myers Squibb, Gilead, Janssen, Merck and ViiV Healthcare)

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	would benefit to all companies whether or not they contributed to the clinical research effort. Even worse, like currently potentially for LFB, they could face the risk of an inclusion of these new indications, while they would be still performing well designed clinical trials in that indication. Indeed, this fading of development is illustrated by the fact that no other company is currently performing clinical trials either in CIPD or in MMN with IVIg. **This is why, based on this unfair potential effect, LFB believes that the proposed revisions will not result in reorienting IVIg clinical trials towards other rare indications:** The pro-innovation effect alleged by the BPWP by orienting the clinical research effort towards other more rare indications, seems unlikely. - Indeed, IVIgs market analysis has revealed that IVIg price competition is mainly based on IVIg differentiation, in terms of therapeutic indications granted and associated volumes. So, over the time, without any differentiation (i.e. with the new proposal including CIDP and MMN in the core SmPC of IVIgs) the decisions of referencing by hospitals will be driven only by the price (as all the products would have the same 5 major indications; PID, ITP, GBS, MMN, CIDP, or new Core SmPC, i.e. ~ 60% of the prescription; the remaining 40% being spread over a big variety of 'small' indications). Even though a little competition would remain, based on minor (i.e. in terms of volume) therapeutic indications, as they would not trigger a volume differentiation (due to their rarity) in the hospital prescription, there are unlikely to change the game in the competition. Otherwise said, a competitor with the sole new Core SmPC, with a lower price, will win quite	This is a moot point as most other main companies have already completed their trials. However, trials with Octapharma and Baxter products are still being performed. See also "ongoing trials" from Cochrane Review 2016 in Section 5. The price discussion is outside the remit of the BPWP however, it should be kept in mind that pricing is also driven by health care systems and their budget, tender systems, and parallel import. Price of IVIG (Table) see below

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	surely, the competition versus another IVIg with an additional rare indication to the SmPC, but with a slightly higher price. Otherwise said again, the potential savings in terms of reimbursement for the hospital versus an off-label prescription in this very rare indication, would not compensate those driven by a competitive price spread over the volume linked to the 5 major main indications. - **An EU exception that could weaken its influence in these diseases:** In addition, in the field of IVIgs, it is noteworthy that US FDA requires the performance of pivotal studies to get registered for each indication targeted, thus confirming its difference in appraising the so called 'established use' in IVIg indications and underlining the absence of consensus in the world with regard this regulatory strategy. As IVIgs are worldwide products, in the scenario of the proposed revision set in place, for a new indication, it should be safer to comply with FDA's requirements, as in the USA a clinical trial is mandatory to get registered, than to try to comply with those, potentially divergent, of EMA, where, in the long run, the indication could be granted for free thanks to its inclusion in the Core SmPC. With the resulting, logical, following consequence: a far greater incentive to perform the related clinical trials in the US rather than in the EU. To decide to open centres in EU would bring the risk of useless efforts (no advantage in the end versus competitors, by inclusion of the indication for all)... The simplest development strategy could be to do the trial in the US only, and then submit these data as they are, in the EU for registration. Thus the proposed measure could also contribute to dry up the clinical research in EU and reduce EMA's influence in the	As mentioned above we could adopt the US system and retrospectively eliminate the granted "established indications" and the entire concept of a core SPC. Whether this would serve the patients and the health system is highly debatable. Whether the coreSPC approach (since 1995) as led to a "drying up" of EU research in this area is also questionable. In the Clinicaltrials.gov website a search for "IVIG trials that are closed" (regardless of reason) showed that 155 trials were performed in the US and 75 in the EU (ratio 2.06), for IVIG trials that are "currently recruiting patients", there are 46 in the USA and 30 in the EU (ratio 1.5). https://clinicaltrials.gov/ct2/results/map?term=IVIG&recr=Open . So the difference of trials currently being performed in the US and the EU is, if anything, possibly diminishing.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	orientation of clinical research in these new indications. **This is why LFB believes, from a regulatory & clinical development strategy standpoint, that the proposed measure regarding MMN & CIDP will not bring any additional incentive, versus the existing ones (ODD, PRIority MEdicine scheme, market exclusivity...), to invest and develop new very rare indications with IVIg. In addition, this proposed revision could be deleterious for clinical research in EU in this field.**	
	Price of IVIGs vary mainly by **country** (hence the possibility of parallel import) **Price of IVIG 10g/100ml (or other where indicated) in Euros** * Prices of parallel importers	
11	***3.2. This could also be deleterious for small EU plasma derived companies such as LFB*** As described above, this revision would probably drive even more rapidly and intensely the IVIg market towards a quasi-exclusively price based competitive market, to the detriment of a competition still based on the quality and diversity of products, and their	Market issues are outside the remit of the BPWP, but as mentioned above the prices do not seem to be determined by indication differences but by differences in health systems, budgets, tender systems and parallel imports.

	Country A	Country B	Country C	Country D	Country E	Country F	Country G	Country H	Country I	Country J	Country K	Country L	Country M
IVIG A (CIDP)	(839*) 997	766	831	-	407	468	546		658	700	592	834 (20g/200ml)	1117
IVIG B (MMN)	(868*) 905	766	504	681	451		583		754	825	616	834 (20g/200ml)	924
IVIG C	851	-	831	-	-			513		749 (50mg/ml 200 ml)		834 (20g 200ml)	511
IVIG D (CIDP)	(920*) 979	790	831	580 (5%/200 ml)	424	472	697	477	651	825		834 (20g/200ml)	822
IVIG E (CIDP)	986	705	-		-		506			749			-

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	differentiation in terms of rare indications. From a general health interest point of view, this raises a real question. Indeed, in this hypothesis, IVIgs could be considered, economically-wise, for the first time, like a commodity, for which only price matters. And in this case, who are the competitors likely to offer the lowest prices? Obviously the biggest ones, because of the critical mass effect (due to their vertical integration with proprietary plasma supply, high batches size in huge plants, worldwide registrations allowing directing their products in the most profitable markets, etc.). Who are the small players in this worldwide market? Notably, 'local' EU players such as LFB. One could argue that doing the clinical trials in these indications and others, is also a charge for the companies that take this initiative, which is likely to be more affordable for big players than for small ones. If it is actually the case, it still makes a key difference: in a competition based on indications (like today), the small players have their chance (depending on their strategy) whereas in a competition based basically on prices (IVIgs are a commodity), this is far more difficult. In this scenario, losing progressively market shares versus big players, small (EU) players will have less resources to develop new indications, which the former will still be able to do, adding, in the end, to their price advantage, an ultimate superiority by differentiation, based on new indications. This resulting in an increased unbalanced competition that will reinforce or foster a trend to oligopolies formation that will, *in fine*, result in a negotiation power shift from payers to few manufacturers, thus possibly in increased prices. It is matter of fact that a progressive concentration has been occurring for the last decades in the plasma industry, like in others, as a natural consequence of an ever more globalized competition. We just want to underline that this	The number of competitors has been contracting over the years; in 1996 there were 24 plasma producers on the market, in 2017 there are 10 (6 of which have the CIDP indication). The only indication that has been added to the established indications in the coreSPC since 1996 has been GBS, so other forces are obviously at work here. The development of oligopolies seems system-inherent (see MRB Patrick Robert http://www.ipopi.org/uploads/Patrick%20Robert.pdf). More than half the "players" already have the indication

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	revision could likely foster and speed up this move, which is probably not in the best interest of patients, in the long run. It is also of importance to note that, if it 'is not the first time that new indications are included in the Core SmPc of IVIgs, this is the first time that the indications included represent around one fourth of the whole prescription of Igs: that is, from an economic standpoint, why this integration is game changing, unlike the previous ones. **This is why LFB believes, from an economic standpoint, that the proposed measure regarding MMN & CIDP could negatively impact the small players by creating an economic useless threat on them (shall we remind that IVIgs are the business driver of fractionators, commanding the plasma call?) versus the existing competition scheme (based on differentiation by indications) and can eventually imbalance the current well established and supplied, competitive IVIgs market.**	CIDP so it is unlikely that the inclusion will be "game changing" The "well-established competitive balance" has in the past years seen the take-over of Talecris by Grifols, of Baxalta by Shire and BPL by Corey. Biotest AG sold to Chinese investor Creat for €1.3bn (April 2017) http://www.goinpharma.com/en/germanys-biotest-ag-sold-to-chinese-investor-creat-for-e1-3bn/ This has nothing to do with indications.
11	**3.3. This is also probably a deleterious proposal for patient access drug in the long run** As of today, all EU member countries have access to several IVIg brand products (manufactured by different companies) including some with CIDP and/or MMN granted indication, and so, without any reported delivery failure or major shortage linked with patient life threatening or disabilities. Therefore, neither from a medical perspective nor a regulatory one, we can consider an « unmet IVIg therapeutic need » in EU, regarding these two indications. Pushing further the reasoning and shifting from a well-established	The BPWP endeavours to keep the GLs up to date The other responses to the concerns have been detailed above and do not have to be reiterated here.

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	IVIg market with many players to an IVIg market with only few players implies that hospitals and patients could suffer from: 1) **less IVIg brands available**: with a product diversity reduced, physicians would probably more hardly find the proper IVIg for the right patient (depending on the patient, some IVIgs are more or less tolerated); 2) **a higher risk of shortage** due to the fact that, once one of the few main suppliers either faces manufacturing issues or decides, for profitability reason, to leave the EU market, it would be all the more difficult for the few remaining ones to compensate the IVIg quantities no more supplied. This could actually become, as well, a national public health concern, if, meanwhile, the local small suppliers would have been weakened and consequently the public efforts requested by the EU commission to the member states to increase their self-sufficiency in these essential medicines, would have been therefore thwarted. **That is why LFB believes the proposed measure regarding MMN & CIDP could have in the long run a negative impact for ensuring the patients' access to these essential specialties.** Contrary to the EMA concisely proposed hypotheses, our analysis is that major risks exist in terms of innovation, with subsequent impacts on diversity of products, aggravation of oligopolistic trends on the market to the benefit of the largest, and ultimately on prices and on the availability of products in Europe. All this being directly against the policy of the European Commission	See above. As mentioned previously, there are many less brands than 20 years ago – this has nothing to do with increase in indications. This is a general issue for all indications and could happen at any time (e.g. Chinese take-over of Biotest). It is deemed system-inherent. The other aspect, not addressed by LFB is the dependency on the US plasma supply which has other reasons, not least of which is the approach by some EU producers to only collect non-remunerated plasma, thereby severely limiting the plasma amount they could otherwise obtain. This might in the long run impact patient's access. In LFB's "analysis" no figures are given to support their speculation on the future trends. It is not in the remit of the BPWP to perform an economic impact analysis. Any GL revision is time consuming - the concept paper came out in Aug 2014 i.e. 3.5 years after the GL became effective (Feb 2011). The conclusion of the current revision process is approx. 7 years after the former version. This is not

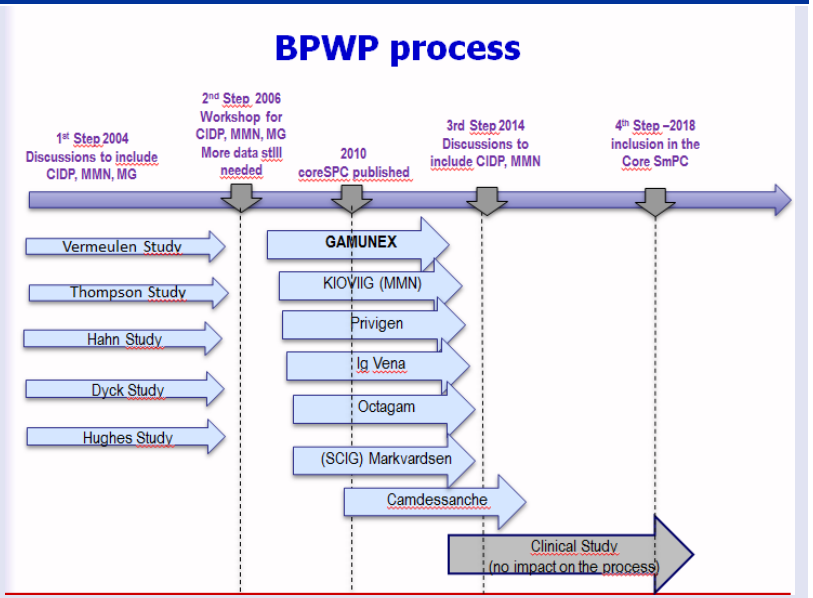
Stakeholder no.	General comment (if any)	Outcome (if applicable)
	and its President. We therefore ask the EMA and the European Commission to produce a detailed impact assessment on all these points, in line with the Commission's best practices before any new legislation or legislative change, that is before modifying the guidelines **In light of the foregoing, LFB considers that the guideline cannot be modified as it is, especially with a so short notice and without having assessed the impact on the EU economy and the patients.**	considered short-term.
11	**4. Proposal for a new Regulatory Pathway** In an attempt to not question the whole existing Core SPC process and taking into consideration the fact that in this proposed revisions regarding MMN and CIDP, the most problematic issues are related to : - the management of the time (contradictory, consecutive, sudden, steps taken) in the process of inclusion of these indications; - the lack, still, of clinical knowledge on some aspects of these pathologies; - the lack of transparency, predictability, and respect of the legitimate expectations of all the stakeholders; - and legal concerns such as the breach of the principal of equal treatment, LFB proposes the following way forward, which would solve all the concerns raised above in our comments. This proposal would also respect both a fair competition between fractionators, and an understandable attempt to increase, over the years, the number of indications that are secured for the patients, avoiding redoing trials	**See section below**

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	that would not bring any new knowledge both on the indication and the particular IVIg tested. Our proposal is the following one: BPWP could 1) **Modify the proposed revision regarding MMN & CIDP** as follows, stating that: once all the ongoing pivotal trials in EU, in these two indications, will be assessed and hopefully granted to all their applicants (which would confirm the validity of the proposed inclusion of these indications in the core SmPC as established indications), a period of 5 years of follow-up will open, as of the last one granted, respectively MMN or CIDP, where: • The safety and efficacy in real life of the authorized products in these indications will be made thanks to pharmacovigilance and, if appropriate through an observatory, to feed a final report to be made at the end of the period, to confirm, or not, the definitive integration of these one or two indications in the Core SmPC of IVIgs. • Only the products registered will be allowed for prescription in these indications (in compliance with legal rules) during the 5 years of surveillance and protection, as a fair reward of their efforts to increase the medical knowledge of these indications by performing these trials. • The companies that would decide to start pivotal trials in these indications as of now, would be of course allowed to, according to current good practices, but this time, knowing clearly that probably at the end of the said	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	period, both MMN & CIDP, could be included in the core SmPC of IVIgs, without dedicated trials required for any future MA application. For LFB, this first Element of our proposal is a prerequisite. 2) **Issue a dedicated guideline / SOP** on how is managed the evolution of the Core SmPC of the IVIGs, that would provide to the economic players respect of the legitimate expectations and legal certainty principles, based on a clarification of the way to elaborate a list of established indications. This SOP could include for instance the description of the whole process, as follows : a) **Step 1 = T0 of the procedure;** the BPWP issues a public statement to the attention of all the stakeholders explaining that as of now, an official period of approximately 10 years opens, at the end of which, provided that the requested scientific and clinical evidences be provided by the manufacturers during this period, the current assessment of a possible inclusion of the concerned indication in the Core SmPC would be confirmed. This statement should contain : i) the clinical and scientific justifications, to date, of such an assumption; ii) the list of scientific and clinical requirements or results expected to trigger the next step of the procedure: e.g. the number of positive pivotal studies to be attain, such and such scientific question explained; the minimal total number of patients successfully treated	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	in pivotal studies, etc. The Guideline /SOP should define as much as possible what are the minimum clinical and scientific requirements to trigger the issuance of such Step 1 statement. b) **Step 2: Intermediate report, at the time when clinical and scientific requirements are actually gathered** (number of clinical trials etc.). The BPWP issues an intermediate report summarizing all the data and science gathered during the period and assessing if these elements confirm or not the Step 1 assumptions. Then, either the process is stopped (evidence of lack of efficacy and safety) - case 1; or restarted for an additional period of enquiry (in case of partial evidences), i.e. back to Step 1 - case 2; or enters into the next step – case 3. Time from Step 1 to Step 2 will be variable, depending on the amount of evidences to gather and the intensity of the scientific and clinical developments efforts of the actors. c) **Step 3: Period of surveillance and protection of 5 years starting, as of the issuance of the intermediate report (step 2, case 3), exactly when the last product for which pivotal clinical trials in EU were ongoing (at the time of step 2) is approved**. The three dispositions described above in point 1) are to be applied (in particular Safety and Efficacy follow-up; prescription for products actually registered only; freedom to start new pivotal studies at risk of regulatory usefulness). d) **Step 4**: **Go-for-inclusion-in-the-Core SmPC final**	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	assessment, at the end of the 5 years confirmation period; BPWP issues a final assessment report based on all the data and science gathered during the last five years. If positive, the indication is included in the Core SmPC with immediate effect. If not, step back to Step 2. 3) **The BPWP should issue a tentative program for the coming years**, ranking the indications that could enter in this process, **defining** the year they could enter this process. This would give the economic players the deserved and useful long term vision, required to make costly decisions such as starting a pivotal study in a (very) rare disease, and in addition to organize their collaboration with research public bodies. See Annex 3: Flow Chart of a Proposal for a new Regulatory Pathway **LFB is convinced that this proposal can address all the goals of the new revision of the guideline regarding MMN and CIDP, as well as the drawbacks, weaknesses, and legal concerns described above.**	
	BPWP discussed process as suggested by LFB and considered that the steps proposed (except for protection for 5 years) were very akin to the steps taken in the process of CIDP and MMN	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
		
		From Cochrane 2016 (excluding fingolimod trial, as it is not relevant to this topic) Trials in progress

	Comparison	Reference
1	Subcutaneous human immunoglobulin versus placebo	Van Schaik 2016; NCT01545076
2	0.2 g/kg versus 0.4 g/kg subcutaneous human immunoglobulin	Markvardsen 2016
3	Fingolimod versus placebo	Hartung 2014; NCT01625182
4	Comparison of 2 different IVIg preparations	Pouget 2016
5	IVIg maintenance versus IVIg taper	Eftimov 2015
6	Dose-response trial of IVIg	Kuitwaard 2016

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Stakeholder no.	General comment (if any)	Outcome (if applicable)
	10% as replacement therapy in primary immune deficiency. A randomized double-blind trial. Int Immunopharmacol. 2003 Sep;3(9):1325-33. Tackenberg B, Jelcic I, Baerenwaldt A, Oertel WH, Sommer N, Nimmerjahn F, Lünemann JD. Impaired inhibitory Fcgamma receptor IIB expression on B cells in chronic inflammatory demyelinating polyneuropathy. Proc Natl Acad Sci U S A. 2009 Mar 24;106(12):4788-92. Thompson N, Choudhary P, Hughes RA, Quinlivan RM. A novel trial design to study the effect of intravenous immunoglobulin in chronic inflammatory demyelinating polyradiculoneuropathy. J Neurol. 1996 Mar;243(3):280-5. Tsai MH, Huang YC, Yen MH, Li CC, Chiu CH, Lin PY, Lin TY, Chang LY. Clinical responses of patients with Kawasaki disease to different brands of intravenous immunoglobulin. J Pediatr. 2006 Jan;148(1):38-43. Van den Berg LH, Kerkhoff H, Oey PL, Franssen H, Mollee I, Vermeulen M, Jennekens FG, Wokke JH. Treatment of multifocal motor neuropathy with high dose intravenous immunoglobulins: a double blind, placebo controlled study. J Neurol Neurosurg Psychiatry. 1995 Sep;59(3):248-52. Van Schaik IN. What's new in chronic inflammatory demyelinating polyradiculoneuropathy in 2007-2008? J Peripher Nerv Syst. 2008;13:258-60 Vermeulen M, van Doorn PA, Brand A, Strengers PF, Jennekens FG, Busch HF. Intravenous immunoglobulin treatment in patients with chronic inflammatory demyelinating polyneuropathy: a double blind, placebo controlled study. J Neurol Neurosurg Psychiatry. 1993 Jan;56(1):36-9. Vucic S, Black K, Baldassari LE, Tick Chong PS, Dawson KT, Cros D.	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
	Long-term effects of intravenous immunoglobulin in CIDP. Clin Neurophysiol. 2007 Sep;118(9):1980-4.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
142-143 (MMN & CIDP)	1	**Comment:** it is acknowledged that recent studies have demonstrated efficacy of certain IVIg products in the treatment of CIDP and MMN. However, because the process for the manufacture of the IVIg product may affect the quality, efficacy and safety of the final product, the different IVIg cannot be considered equivalent. Therefore the efficacy and the safety of the IVIg product in the CIDP and MMN indications need to be demonstrated by confirmatory data. _____ CSL believes that adding CIDP and MMN to the established indications would significantly reduce the incentive for industry to conduct large studies for new Ig-indications. For industry it is critical that an investment in new indications can be leveraged **Proposed change (if any):** remove the 2 indications MMN and CIDP	IVIGs are not considered equivalent, nor are different batches from one product; IVIGs are considered sufficiently akin to one another to warrant a class effect in terms of the active ingredient for efficacy purposes. The Eur. Pharmacopeia Monograph has to be adhered to produce Human Normal Ig. A number of international GLs on clinical use refer to IVIG as a class. Furthermore switches of products (tender systems, Marketing Authorisation withdrawal or shortages) are possible without “lack of efficacy” occurring. _____ Not accepted. Although the pecuniary aspects are beyond the scope of the GL, one should bear in mind that due to the extrapolation principle of the initial core SPC (1995), companies have not had to perform any studies in SID, GBS, Kawasaki and could leverage this to their benefit. Furthermore, common studies could be performed by the industry, thereby sharing the costs and the spoils.
171-172(SID poso)	1	**Comment**: we agree to the proposed dose (0.2-0.4 g/kg every three to four weeks) in SID as a starting dose. However, in SID, as in PID, the dose should be	Accepted and added

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		adapted to the individual patient's needs. Some patients may require a higher dose to remain infection free. We propose a text that allows physician to make this dose adjustment. This recommendation is also based on the opinion of experts in the field that consulted. **Proposed change (if any):** Secondary immunodeficiencies (as defined in 4.1.) The recommended starting dose is 0.2-0.4 g/kg every three to four weeks. IgG trough levels should be measured and assessed in conjunction with the incidence of infection. Dose should be adjusted as necessary to achieve optimal protection against infections, an increase may be necessary in patients with persisting infection, a dose decrease can be considered when the patient remains infection free.	
184-185 (Kawasaki)	1	**Comment:** the treatment might be the first time for patients who might have concomitant risk factors for developing ADRs and to decrease possible tolerability issues, CSL proposes to keep the previous text **Proposed change (if any):** 1.6-2.0 g/kg should be administered in divided doses over two to five days or 2.0 g/kg as a single dose. Patients should receive concomitant treatment with acetylsalicylic acid.	Not accepted. Meta-analyses showed that single dose is more effective (J. Newburger et al. 2004) http://pediatrics.aappublications.org/content/114/6/1708.full#sec-21 *A variety of dose regimens have been used in Japan and the United States. Two meta-analyses* have demonstrated a dose-response effect, with higher doses given in a single infusion having the greatest efficacy* *Patients should be treated with IVIG, 2 g/kg in a single infusion (evidence level A), together with aspirin*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
			*Durongpisitkul K, Gururaj VJ, Park JM, Martin CF. The prevention of coronary artery aneurysm in Kawasaki disease: a meta-analysis on the efficacy of aspirin and immunoglobulin treatment. Pediatrics. 1995;96 :1057– 1061 *Terai M, Shulman ST. Prevalence of coronary artery abnormalities in Kawasaki disease is highly dependent on gamma globulin dose but independent of salicylate dose.* J Pediatr. 1997*;*131 *:*888*–* *893*
187-202 (SID, Kawasaki, MMN & CIDP poso)	1	**Comment:** from above 142-143 comment, posology for MMN and CIDP are to be removed. SID and Kawasaki posology are to be updated. **Proposed change (if any):** remove 187-194 and update accordingly the table between 196-202 for MMN, CIDP, SID and Kawasaki as per above comments.	See above
Line 31	2	**Comment:** QRD needs to be explained, as it is the first time that it appears on the document **Proposed change (if any):** "the Quality Review of Documents (QRD) product information template."	Added suggestion
Line 34	2	**Comment:** Replace "very useful" by "necessary" **Proposed change (if any):** "It is very useful necessary to provide information…"	Added suggestion However, the physician normally has access to the SPC…

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 256 to 260	2	**Comment:** One additional reason for an adverse reaction can be an “undiagnosed infection”. We suggest adding a new bullet point on this idea. **Proposed change (if any):**	Partly accepted and reworded
Line 302-303	2	**Comment:** Does it make a difference between 5% and 10% products? **Proposed change (if any):**	One head-to-head study with 5% and 10% (Flebogamma Dif SPC): In a Post-authorisation Safety Study that included 66 patients, Flebogamma DIF 100 mg/ml showed a higher rate (18.46%, n=24/130) of infusions associated with potentially related adverse events than Flebogamma DIF 50 mg/ml (2.22%, n=3/135). However one subject treated with Flebogamma DIF 100 mg/ml presented mild episodes of headache in all infusions and one more patient had 2 episodes of pyrexia in 2 infusions. It is worth considering that these 2 subjects contributed to the higher frequency of infusions with reactions in this group. There were no other subjects with more than 1 infusion with adverse reactions in both groups. For Intratect 5% and 10% there are some differences in the 2 tables of the SPC however, the sample sizes are also different so precise conclusions cannot be drawn.
Line 319-320	2	**Comment:** Does it make a difference between 5% and 10% products? **Proposed change (if any):**	See above

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 347	2	**Comment:** Why use the term “injection”? Throughout the document the word “administration” is used. **Proposed change (if any):** “After injection administration of immunoglobulin…”	Suggestion added.
Line 366	2	**Comment:** Should diagnosed patients receive these vaccines at all? **Proposed change (if any):**	Some patients (other than PID and some SID) may be candidates for live vaccines, this is the reason that this paragraph can remain unchanged
Line 389	2	**Comment:** Dosage might need to be adjusted for pregnant women. **Proposed change (if any):**	4.2 already mentions that the dose may have to be individualised, this is deemed to be sufficient
Lines 412 to 426	2	**Comment:** Precision should be given to terms such as “occasionally” or “very rarely” **Proposed change (if any):**	Section has been reworded. Very rarely and rarely are already classified terms
Line 443	2	**Comment:** terms such as “very common” “common”, “uncommon”, “rare” and “very rare” should be further defined and frequency rates (1 in X number of people) should be included. **Proposed change (if any):**	The rates are already included. The table now includes frequency per patient and frequency per infusion
Line 516	2	**Comment:** we should reinstate that it should not be mixed with any other immunoglobulin medicinal	Added suggestion into text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		product. **Proposed change (if any):** "… must not be mixed with other medicinal products, nor with any other IVIg products"	
142-143	5	**Comment:** The available clinical data for the indications CIDP and MMN is considered sufficient to establish these indications without further clinical data to be provided. This is underpinned by a review by Cherin & Cabane (2010) which appreciates the safety and tolerability differences of human normal immunoglobulins but also emphasizes the similarity in terms of efficacy. Existing clinical trials and literature reviews conducted for CIDP (Lozeron & Adams, 2011; Nobile-Orazio et al., 2012; Querol, 2013) and MMN (Van den Berg-Vos et al., 2002; Léger, 2001, 2008; Meuth & Kleinschnitz, 2010), thoroughly prove the efficacy of human normal immunoglobulin in these indications. Main guidelines, such as the European Federation of Neurological Societies/Peripheral Nerve Society guideline (2010), the American Academy of Neurology guideline (2012) or the German consensus paper on the use of intravenous immunoglobulins in Neurology (Stangel & Gold, 2011) confirm that the use of human normal immunoglobulin in CIDP and MMN is accepted clinical practice. In the CHMP Assessment Report on the MMN label	Agreed

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		extension of Kiovig (Baxter) from 2011, the Committee for Medicinal Products for Human Use accepted the efficacy data also considering additional data of other human normal immunoglobulins. In the conclusion on the clinical efficacy, it is stated that: "Overall, results for KIOVIG from 2 prospective studies with this product and **supportive data from randomized, placebo-controlled MMN trials with other IVIg products** provide evidence indicating that KIOVIG is effective in the treatment of MMN." (CHMP Assessment Report, 2011, p.26). Literature Recently, some clinical findings support the recommendation of IVIG as a first line treatment of MMN, especially because other effective therapies are not available (Koski, 2014; Léger, 2014; Kuitwaard, 2015). It could be shown that antiinflammatory and immunomodulatory effects of IVIg influence the course of disease of peripheral neuropathies (GBS, CIDP, MMN) positively (Lünemann 2015). Recently, an analysis of the use of different IVIg brands did not show differences in the response to therapy in patients with CIDP and MMN (Gallia, 2016). Finally, it should also be considered that the patient population of these therapeutic indications is limited	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		and further studies in this population do not seem to be warranted. References: • Chérin, P., Cabane, J. "Relevant criteria for selecting an intravenous immunoglobulin preparation for clinical use." Biodrugs (2010) 24: 211-223. • Gallia F. et al. "Efficacy and tolerability of different brands of intravenous immunoglobulin in the maintenance treatment of chronic immune mediated neuropathies". J Periph Nerv Syst (2016) 21: 82-84. • Léger, J.-M. et al.: Intravenous immunoglobulin therapy in multifocal motor neuropathy. A double-blind, placebo-controlled study, Brain (2001) 124: 145-153 • Léger, J. M., et al. "Intravenous immunoglobulin as short-and long-term therapy of multifocal motor neuropathy: a retrospective study of response to IVIg and of its predictive criteria in 40 patients." J Neurol Neurosurg Psychiatry (2008) 79: 93-96. • Léger, J.-M. "Immunoglobulin (Ig) in multifocal motor neuropathy (MMN): update on evidence for Ig treatment in MMN". Clin Exp Immunol (12014) 178:42-44 • Lozeron, P., Adams, D. "Advances in the treatment of chronic inflammatory demyelinating	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		neuropathies in 2010." J Neurol (2011) 259: 1737-1741. • Lünemann, J. D. et al.: "Intravenous immunoglobulin in neurology – mode of action and clinical efficacy". Nat Rev Neurol (2015)11:80-89. • Koski, C.L. "Treatment of multifocal motor neuropathy with intravenous immunoglobulin". J Clin Immunol (2014) 34 (Suppl 1): S127-S131 • Kuitwaard K. et al. "Intravenous immunoglobulin response in treatment-naive chronic inflammatory demyelinating polyradiculoneuropathy". J Neurol Neurosurg Psychiatry (2015) 86:1331-1336. • Meuth, S.G., Kleinschnitz, C. "Multifocal motor neuropathy: update on clinical characteristics, pathophysiological concepts and therapeutic options." Eur Neurol (2010) 63: 193-204. • Nobile-Orazio, E., et al. "Intravenous immunoglobulin versus intravenous methylprednisolone for chronic inflammatory demyelinating polyradiculoneuropathy: a randomised controlled trial." Lancet Neurology (2012) 11: 493-502. • Patwa, H. S., et al. "Evidence-based guideline: Intravenous immunoglobulin in the treatment of neuromuscular disorders Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology." Neurology (2012) 78: 1009-1015.	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		• Querol, L., et al. "Long-term outcome in CIDP patients treated with IVIg: A retrospective study." Muscle Nerve (2013) 48: 870-876 • Van den Berg-Vos, R. M. et al.: Multifocal motor neuropathy: Long-term clinical and electrophysiological assessment of intravenous immunoglobulin maintenance treatment, Brain (2002) 125: 1875-1886 • Van den Bergh, P,and the EFNS/PNS CIDP Task Force. "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—first revision." Eur J Neurol (2010) 17: 356-363. • Stangel, MGold, R. "Einsatz intravenöser Immunglobuline in der Neurologie." Der Nervenarzt (2011) 82: 415-430.	
160-161 165	5	**Comment:** The dose regimen should achieve a trough level of IgG (measured before the next infusion) of at least 6 g/ l ... The dose required to achieve a trough level of 5-6 g/l is ...	6g/L - agreed

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Correction of 5-6 g/l to 6 g/l in line number 165 in order to reflect the current recommendation in line 160	
191	5	Multifocal Motor Neuropathy (MMN) In the table between lines 196 and 197 MMN is marked with an asterisk but the asterisk is missing in line 191 **Proposed change (if any):** Multifocal Motor Neuropathy (MMN)*	Asterisk added. Later removed as footnote was added into the main text
196 - 197	5	The table "the dosage recommendations ..." does not reflect correctly the changes in lines 159 to 193. Proposed change (if any): The table "the dosage recommendations ..." has to be revised according to the changes in lines 159 to 193 in order to reflect the current recommendations.	Reworded
221	5	Hypersensitivity to the active substance or to any of the excipients (see section 4.4). **Proposed change (if any):** The excipients are described in section 6.1 (List of excipients) therefore the reference should be revised to ...(see section 6.1).	Addition is acceptable
142-143 (MMN &	6	It is acknowledged that recent studies have demonstrated efficacy of certain IVIg products in the	Same wording as CSL - see comment to CSL

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
CIDP)		treatment of CIDP and MMN. However, because the process for the manufacture of the IVIg product may affect the quality, efficacy and safety of the final product, the different IVIg cannot be considered equivalent. Therefore the efficacy and the safety of the IVIg product in the CIDP and MMN indications need to be demonstrated by confirmatory data. Grifols considers that adding CIDP and MMN to the established indications would significantly reduce the incentive for industry to conduct large studies for new Ig-indications. For industry it is critical that an investment in new indications can be leveraged **Proposed change (if any):** remove the 2 indications MMN and CIDP	
171-172(SID poso)	6	**Comment:** Grifols agrees to the proposed dose (0.2-0.4 g/kg every three to four weeks) in SID as a starting dose. However, in SID, as in PID, the dose should be adapted to the individual patient's needs. Some patients may require a higher dose to remain infection free. We propose a text that allows physician to make this dose adjustment. This recommendation is also based on reference clinical guidelines for immunoglobulin use and the opinion of experts in the field that consulted. References: Department of Health. Clinical guidelines for immunoglobulin use. 2nd edition update. Department of Health; 2011.	Accepted. (Same wording as CSL - see comment to CSL) N.B. Both references quoted by Grifols (UK and Australian GL) refer to IVIG as appropriate for CIDP and MMN (level 1 evidence)

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_129617 National Blood Authority. Criteria for the clinical use of intravenous immunoglobulin in Australia, 2nd ed. National Blood Authority; 2012. https://www.blood.gov.au/ivig-criteria Proposed change (if any): Secondary immunodeficiencies (as defined in 4.1.) The recommended starting dose is 0.2-0.4 g/kg every three to four weeks to obtain a trough level of at least 6 g/l or within the normal range for the population. IgG trough levels should be measured and assessed in conjunction with the incidence of infection. Dose should be adjusted as necessary to achieve optimal protection against infections, an increase may be necessary in patients with persisting infection, a dose decrease can be considered when the patient remains infection free.	
184-185 (Kawasaki)	6	**Comment:** The treatment might be the first time for patients who might have concomitant risk factors for developing ADRs and to decrease possible tolerability issues, Grifols proposes to keep the previous text. Proposed change (if any): 1.6-2.0 g/kg should be administered in divided doses over two to five days or 2.0 g/kg as a single dose. Patients should receive concomitant treatment with acetylsalicylic acid.	See above: Two meta-analyses have demonstrated a dose-response effect, with higher doses given in a single infusion having the greatest efficacy (Newburger http://pediatrics.aappublications.org/content/114/6/1708)

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
187-202 (SID, Kawasaki, MMN & CIDP poso)	6	**Comment:** From above 142-143 comment, posology for MMN and CIDP are to be removed. SID and Kawasaki posology are to be updated. Proposed change (if any): Remove 187-194 and update accordingly the table between 196-202 for MMN, CIDP, SID and Kawasaki as per above comments.	See comment above
45-47 (SID, Kawasaki, MMN & CIDP)	6	**Proposed change (if any):** Update the introduction following the proposed changes.	N. a
15	7	**Comment:** The rationale on which the dosing based on bodyweight requiring adjustment in under or overweight patients, needs to be clearer. There is no definitive opinion/ consensus on dosing based on adjusted body weight. Dosing by clinical outcome would be the most appropriate strategy to use. **Proposed change (if any):** Dosage adjustments based on body weight in underweight or overweight patients should only be rough guides and each patient's optimal IgG level and dose should be determined individually by their clinical response.	Agreed. The current text states that: *The dose may need to be individualized for each patient dependent on the clinical response*. As the currently ongoing discussions (and data set) on dosing by ideal body weight have not yet sufficiently matured, it was difficult to give exact recommendations. Therefore a general statement was included: "*Dose based on bodyweight may require adjustment in underweight or overweight patients".*
130-132:	7	**Comment:** the indication in SID is very restrictive. LFB suggests	The revised text is actually an extension of the former indications and encompasses more areas of possible

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Ineffective antibiotic treatment not to be required as the risk of lack of efficacy of repeated antibiotic treatments may be prevented by Ig replacement therapy. **Proposed change (if any):** "Secondary immunodeficiencies (SID) in patients who suffer from severe or recurrent bacterial infections, ineffective antibiotic treatment and either proven specific antibody failure (PSAF)* or serum IgG level of <4 g/l"	treatment (the antibiotic failure was also part of the former wording…) IPFA has not changed the wording….
156	7	**Comment:** The rationale on which the dosing based on bodyweight requiring adjustment in under or overweight patients, needs to be clearer. There is no definitive opinion/ consensus on dosing based on adjusted body weight. Dosing by clinical outcome would be the most appropriate strategy to use. **Proposed change (if any):** Dosage adjustments based on body weight in underweight or overweight patients should only be rough guides and each patient's optimal IgG level and dose should be determined individually by their clinical response.	See above
162	7	**Comment:** Missing full stop in sentence. **Proposed change (if any):** …to occur. The	Added.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		recommended…	
189	7	**Comment:** We think that the recommendation for the maintenance dose of CIDP therapy (i.e., 1 g/kg every 3 weeks) is too rigid. According to the European Federation of Neurological Societies (EFNS) and the Peripheral Nerve Society (PNS), 15 to 30% of patients require only a single course of IVIg for the treatment of their CIDP. In patients who respond to IVIG, the course dose and the course frequency should be individualised. **Proposed change (if any):** We suggest replacing the line 189 by more flexible recommendation. For instance: "The response should be monitored after each course. In case of lack of efficacy after 3 courses, cessation of treatment should be considered. Beyond 4 months, continuation of treatment should be decided by the physician on the basis of patient's overall response and response duration. The dose and dose interval may be adapted according to the individual course of the disease. Frequently prescribed maintenance doses: 1 g/kg over 1-2 consecutive days every 3 weeks. every 2 to 4 weeks or 2 g/kg over 2-5 consecutive days every 4 to 8 weeks"	The dose is based on studies seen so far – however individual tailoring may be appropriate Australian GL supports 6 month trial period: *IVIg should be used for 3 to 6 months (3 to 6 courses) before determining whether the patient has responded. Most individuals will respond within three months unless there is significant axonal degeneration whereby a six-month course will be necessary.* *If there is no benefit after 3 to 6 courses, IVIg therapy should be abandoned.*

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
191	7	**Comment:** Insert asterisk as per Line 187 and repeated in Table. **Proposed change (if any):** Multifocal Motor Neuropathy (MMN)*	Added asterisk. Later removed as footnote was added into the main text
196 Page 7: Table 1st line 3rd column	7	Comment: Frequency of injections in PID. There a discrepancy between text (line 160) and table: "Trough level of at least 5-6 g/L" should be replaced by "Trough level of at least 6 g/L" Proposed change in the table: "Trough level of at least 6 g/L"	See above
196 Page 7: Table; Line 7 & 8 2nd column	7	**Comment:** for CIDP and for MMN the starting doses should be presented before the maintenance doses (2nd column). **Proposed change (if any):** Chronic inflammatory demyelinating polyneuropathy (CIDP)*: ~~maintenance dose: 1 g/kg~~ starting dose: 2 g/kg in divided doses over 2-5 consecutive days — every 3 weeks over 1-2 days in divided doses over 2-5 days maintenance dose: 1 g/kg in divided doses over 1-2 consecutive days or 2 g/kg in divided doses over 2-5 consecutive days Multifocal Motor Neuropathy (MMN)*: starting dose: 2 g/kg in divided doses over 2-5 consecutive days — every 2-4 weeks or every 4-8 weeks over 2-5 days maintenance dose: 1 g/kg in divided doses	Amended.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		over 1-2 consecutive days or 2 g/kg in divided doses over 2-5 consecutive days.	
265-269 4.4 Special warnings and precautions for use	7	**Comment:** 4.4 Special warnings and precautions for use: The patient monitoring should be performed in the hospital in case of switch from one IVIg preparation to another. **Proposed change (if any):** "…, patients switched from an alternative IVIg product ……should be monitored at hospital during the first infusion and …"	Added proposal into text.
339	7	**Comment:** Query absence of underlining congruent with other headings. Although this paragraph contains a <product specific > statement **Proposed change (if any):** Neutropenia/Leukopenia	Added.
443	7	**Comment:** Link provided in document takes one to a page stating that it does no longer exists: (http://www.ema.europa.eu/ema/htms/human/qrd/docs/HappendixII.doc) **Proposed change (if any):** Correct hyperlink.	Link updated