16 December 2021
EMA/20937/2021

Blood Products Working Party (BPWP)

Overview of comments received on Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg) (EMA/CHMP/BPWP/94033/2007 rev. 4)

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

Stakeholder no.	Name of organisation or individual
1	Prof. Dr. Peter Van den Bergh; Neuromuscular Reference Centre UCL Saint-Luc 1200 Brussels
2	Plasma Protein Therapeutics Association (PPTA)
3	Ernestina Santos, Neurology Department, Hospital Santo António, Centro Hospitalar Universitário do Porto, Portugal
4	Netherlands Medicines Evaluation Board (MEB)
5	Pfizer
6	Sanofi
7	Mateja Baruca, MD, neurologist
8	Prof. Massimo Filippi, Neuroimaging Research Unit, Ospedale San Raffaele, Italy
9	Prof. Filipe Palavra, Hospital Pediátrico – CHUC, Portugal
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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	Comment: GBS, CIDP, MMN Proposed change (if any): Myasthenia Gravis responds well to IVIG in patients with myasthenic crisis. I propose to add this indication.	See below Lines 77-78
2	For the span or range of numbers a dash should be used instead of hyphen (e.g., 0.8–1 g/kg, for 2–5 days) throughout the text.	Accepted.
3	I agree with the content of the document.	Greatly appreciated.
4	The proposal to include an indication and posology for Measles post-exposure prophylaxis for susceptible persons in the IVIg Core SmPC, provided the antimeasles antibody titre threshold as laid out in the IVIg Clinical Investigation Guideline is added to the product specification, is supported. However, the inclusion in the indication of *"in whom active immunisation is contraindicated"* is not fully understood. Although treatment guidelines generally recommend vaccination in case of measles exposure when the subject is not immunosuppressed, there are situations where vaccination is not possible or advisable i.e. during pregnancy or in young infants. It is not considered justified or necessary to restrict the indication to those in whom active immunisation is contraindicated. The recommendation to take	See below Line 64.

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	national recommendations into consideration can adequately accommodate national positions on active immunization. --- It is suggested that a short justification, e.g. with reference to the publications or data sources consulted, should be given in both guidelines for the addition to the product specification of *"0.36 x CBER Standard lot 176 anti-measles antibody titre threshold"* and for the target serum level of measles antibodies of >240 mIU/mL	--- Accepted. Added reference (FDA letter) and WHO Manual.
5	It would be helpful if the Agency could either expand the scope of the current guideline to cover other IVIg replacement therapies such as fragments or recombinants, or if a separate guideline on the development of these therapies could be developed. --- It would be helpful to provide some guidance on how clinical development can bridge between IV and SC/IM dosing (with reference to "Clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCIg/IMIg) CHMP/BPWP/410415/2011 Rev. 1)". For example, if efficacy was demonstrated in an open-label study using IV dosing, it would be helpful to clarify whether a placebo-controlled (or active comparator) study would be required to demonstrate SC efficacy for the same	The current scope will not be expanded to cover modified IVIGs. In the past this was actively excluded as e.g. Fc-modified IVIGs did not show the same efficacy in ITP. Recombinant IVIGs such as Pfizer is developing are of great interest and if/once matured may warrant the development of a separate GL. For internal info: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6413835/ --- Although this suggestion is appreciated, it will probably have to be looked at on a case-by-case basis. A review of the SCIG Guideline and coreSmPC is foreseen in the BPWP workplan. However, the interruptions occurring through Brexit and the resulting Business Continuity Plan and reorganisation of the EMA in addition to COVID 19 have put this work on hold until after September 2021.

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	indication, or if a PK/PD trial would suffice. If this guidance is adopted, will there be a review (and potential update) of the "Clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration (SCIg/IMIg) CHMP/BPWP/410415/2011 Rev. 1)"?	
6	In the Executive Summary, we would appreciate if the EMA could clarify the reason why the use of immunoglobulins for the treatment of measles post exposure prophylaxis for susceptible persons in whom active immunization is contraindicated. We found that later in the document, there is reference to the use of IgG in other rare conditions. Does this statement indicate that this particular application (treatment of measles post exposure) is out of scope in reference to this guidance? --- Under the Scope section, we suggest to provide more information around the products which are excluded from the scope of the guideline (Guideline does not relate to fragmented or chemically modified products.) At a minimum, are there separate guidelines related to other modified IgG products? In other words, we would	Given the rising number of measles outbreaks in the EU (prior to the COVID crisis), the current revision was to only address the aspect of measles pre and post exposure prophylaxis. Furthermore, it was estimated that due to COVID over 117 million children in 37 countries may miss out on receiving life-saving measles vaccine. Measles immunization campaigns in 24 countries were delayed (April 2020). (Statement by the Measles & Rubella Initiative: American Red Cross, U.S. CDC, UNICEF, UN Foundation and WHO (14 April 2020)) **Other indications were not to be covered at the time of this revision.** --- This GL only applies to human derived IgG (Guideline on the clinical investigation of human normal immunoglobulin for intravenous administration (IVIg)) There are no GLs related to modified products.

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	like to know if this guideline only applies to human derived IgG? --- In section 7, only one reference is provided. This does not provide a sense around capture of wide background data to support this set of guidelines. We suggest to include this article (U. Jäger, W. Barcellini, C.M. Broome, et al., Diagnosis and treatment of autoimmune hemolytic anemia in adults: Recommendations from the First International Consensus Meeting, Blood Reviews(2019), https://doi.org/10.1016/j.blre.2019.100648) in the references of the Guideline.	--- Not accepted. This article is on different subsets of AIHA which is not an established indication in the IVIG coreSPC. Obviously, over the > 50 years of use of IVIGs in the established indications a wide host of articles could be quoted. The reference to the ITP International Working Group Report (Blood. 2009;113:2386-2393) is because this formed the basis of the revision of the GL for ITP. We have now added the WHO Manual and FDA letter to outline the basis for the measles PEP requirements.
7	The content of the guideline is adequate and in my opinion, no changes are required.	Greatly appreciated.
8	Prof. Filippi has no comments.	Greatly appreciated.
9	I read the guideline and I have no comments to make. It seems good to me.	Greatly appreciated.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 36	3	Comment: Proposed change (if any): should be polyradiculoneuropathy	Accepted
Lines 63-64	2	Comment: The word "treatment" should be omitted from the sentence. Proposed change: '…recommendation to use immunoglobulins for the measles post-exposure prophylaxis…'	Accepted.
Line 64	4	Comment: there are situations where vaccination is not possible or advisable i.e. during pregnancy or in young infants. It is not considered justified or necessary to restrict the indication to those in whom active immunisation is contraindicated. The recommendation to take national recommendations into consideration can adequately accommodate national positions on active immunization. Proposed change:	Partly accepted. The following text has been added in the guideline: ….in whom active immunisation is contraindicated or is not advised. The following text has been added in section 4.1 of the core SmPC: Consideration should also be given to official recommendations on intravenous human immunoglobulin

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		persons in whom active immunisation is not possible or advised according to national recommendations.	use in measles pre-/post exposure prophylaxis and active immunisation.
Lines 77-78	1	Comment: Myasthenia Gravis responds well to IVIG in patients with myasthenic crisis. I propose to add this indication. Proposed change (if any): Add Myasthenic crisis	Not accepted. However, the point is well taken and appreciated. Given the rising number of measles outbreaks in the EU (prior to the COVID crisis), the current revision was to only address the aspect of measles post exposure prophylaxis. The indication MG exacerbations was authorised in 2/2020 for Gamunex (IVIG-C) after the company (Grifols) submitted an adequately performed study. It has been the practice within the BPWP to have a number of well-designed studies with various IVIGs proving efficacy before adding an indication to the "established indications" in the Guideline and coreSmPC. The Cochrane Review from 12/2012 concluded that three RCTs addressed the treatment of MG worsening or exacerbation and demonstrated the efficacy of IVIg in this specific situation: • One compared with placebo (Zinman 2007 – also used IVIG-C) or • Two compared with plasma exchange (Barth 2011 used Gamunex; Gajdos 1997 used Gammachron) Possibly, when more well designed studies with other products become available, this indication could be discussed for addition to the "established indications" in a future revision of the IVIG GL and coreSmPC.

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Line 78	2	Comment: Please correct 'poly-radiculoneuropathy' to 'polyradiculoneuropathy'	Accepted.
Line 78	3	Comment: Proposed change (if any): should be polyradiculoneuropathy	Accepted.
Line 82	3	Comment: Proposed change (if any): should be follow-up	Accepted.
Lines 106-107	2	Comment: Section 5.10 'Studies in elderly patients' is removed from this revision/ revision 4. However, the ICH Topic E7 is still cited in 'Legal basis and relevant guidelines' Proposed change: Section 5.10 is to be removed, otherwise it is to be corrected (it is not clear what is 123 in "the **123** Questions and Answers" stands for).	Accepted.
Line 131	3	Comment: Proposed change (if any): to batch is repeated	Partly accepted. Corrected: with regards ~~to~~ batch-to-batch consistency.
Line 148	2	Comment: There is an incorrect cross-reference to the reference for Section for measles virus post-exposure	Accepted.

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		prophylaxis. Proposed change: Change reference to Section to 5.3.4 instead of 5.3.7.	
Line 148	10	Comment: Reference to section 5.3.7 (does not exist) should be replaced with reference to section 5.3.4 in the document.	Accepted.
Line 150	6	In section 5.1.1– We would like more clarifications around the "Anti-complementary activity".	See Eur. Ph. Monograph 918 and Test for anti-complementary activity of immunoglobulin (2.6.17)
Line 166	10	Comment: Clarification is requested as to whether the required sample size 40/20 is also required for other indications than PID.	Comment: No, the sample size 40/20 is not required for other indications than PID. For ITP it is 30 adult chronic patients. For other indications this would have to be looked at on a case-by-case basis, possibly through a Scientific Advice procedure.
Line 180 -185	6	In section 5.2.2 – We would like more clarifications regarding Patients already stabilized on IgG treatment. In other words, we would be grateful if EMA could provide general clinical determinants around what the EMA considers "stabilized".	In 5.2.1 it is stated that "*The IgG trough levels of the investigational product should be assessed prior to each infusion over a period of 6 months, starting after 5-6 administrations of the product".* PK data in patients after 5-6 administrations of IVIG are considered stabilised.
Line 200	10	Comment: Clarification on the reasons for requiring at least 40 subjects and half of them children would be appreciated.	The primary endpoint mainly defines this approx. sample size. As numerous forms of PID are already prevalent in younger patients, data to be gathered in children are considered necessary to support the MAA.
Line 202 - 203	6	Comment: We would be grateful if you could clarify this statement : If the recommended primary endpoint	The recommended primary endpoint is the number of serious bacterial infections per patient per year (see below for

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		is less than 1 infection per patient and year, as stated in the guideline, so we understand that the number of infections is either 0 or 1 per patient and per year. Is that correct?	Statistical considerations). Statistical considerations The primary endpoint should be the incidence of serious bacterial infections per person per year, and the objective should be to show that in treated patients the incidence is less than 1.0 per person per year. Although the sample size/power calculation is at the applicant's risk, the following is recommended: The number of patients to be included into the study might exceed 40 as the study should provide at least 80% power to reject the null-hypothesis of a serious bacterial infection rate (infection per patient per year) greater or equal 1 by means of a one-sided test and a Type I error of 0.01.
Line 202-203	6	We would be grateful if EMA could provide more details on the rationale behind the efficacy evaluations requiring a one-year duration clinical trial. Can this one-year duration be reduced in some cases? (reduced to 6 months for example?)	This cannot be reduced to 6 months as there are fluctuations in infections rates and e.g. on occasion this has led to difficulties comparing a predecessor product with data collected in the summer to a new product with data from the winter months.
204	10	Comment: Please clarify what does 'less than 1.0 infection/subject/year' mean? It is unclear if it relates to the trial sample size or the null hypothesis.	Comment: less than 1.0 infection/patient/year – this refers to the null hypothesis, which in turn drives the sample size. In most studies for the entire population this results in an SBI rate of well below 1/pt/y
Line 205	6	Proposed change: patient instead of subject	Accepted.

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Line 214	10	Comment: If would be helpful if the term "hospitalisations" would be specified, e.g. to "infection related hospitalizations" It would be helpful if the definition of "fever episodes" would be clarified (e.g. what temperature, for how long, etc).	Not accepted It is up to the applicant to provide details on the reasons for the hospitalisations (it could also be for side-effects which would be relevant in the context of safety evaluation) – The same applies to fever episodes.
Line 217	6	Proposed change: patient instead of subject.	Accepted.
Lines 218-219	5	Comment: Typo in this section: In this section the statistical parameters indicate the need for 80% Power and a "Type 1 Error of 0.01". Proposed change (if any): Type I error of ~~0.01~~ 0.1.	Not accepted, 0.01 is correct. (see also FDA Guidance to Industry)
Line 218	6	Comment: We would suggest to add bacterial to the "serious infection rate" statement. Proposed change: serious bacterial infection rate	Accepted.
Line 218	6	Comment: The Primary endpoint is the number of serious bacterial infections (less than 1.0 infection/subject/year). We would appreciate if you could clarify that the mean value of bacterial infections >= 1.0 is per year?	Partly accepted. <u>Statistical considerations</u> The primary endpoint should be the incidence of serious

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		Besides, the variability source should be indicated. However, should we expect a heterogeneity of number of infections among the patients? Sanofi considers this is not the case. Indeed, with a mean value of 1 and a variability of the primary endpoint which could be quite low, then it would seem difficult to reach N=40 patients.	bacterial infections per person per year, and the objective should be to show that in treated patients the incidence is significantly smaller than 1.0 per person per year. Although the sample size/power calculation is at the applicant's risk, the following is recommended: The number of patients to be included into the study might exceed 40 as the study should provide at least 80% power to reject the null-hypothesis of a serious bacterial infection rate (infection per patient per year) greater or equal 1 by means of a one-sided test and a Type I error of 0.01.
Line 219	6	Comment: We would appreciate if the EMA could clarify the rationale behind the choice of the alpha risk error (false positive) which is chosen as minimal value 0.01 and not 5% which is the classical value?	Comment: This has been the testing strategy to define the alpha risk error since 2008 accepted by both the FDA and EMA and the plasma producing industry in numerous previous consultations.
Line 239	10	Comment: It would be good to give the rationales for the required sample size of 30 subjects.	This sample size was chosen in the past for pragmatic reasons (balancing between feasibility/patient availability and sample size enabling sufficiently informative trials). Data show that results are largely comparable between products (except for Fc modified products) For consistency reasons this will also allow future comparisons against results from previous studies. Any other sample size should be justified by the applicant Thus, it is recommended that the number of patients is maintained.
Line 240	6	In section 5.3.3 ITP, References are given for adult	Not accepted

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		patients, but given that ITP is different in the pediatric population, we would welcome a separate set of guidelines for the pediatric population, which would facilitate the pediatric development	This was discussed with PDCO in 2008 at the time of the revision of the wording for ITP and they agreed that in the case of IVIG extrapolation from adults to children was acceptable and no separate studies (or GLs) were requested
Line 241	3	Comment: Proposed change (if any): should be <30x10*9/l	Accepted.
241 262 264 266 268 269	10	Comment: Platelet count should be corrected from "> YY x 109/l" to "> YY x 10^9/l"	Accepted.
244	10	Comment: Quite often, sponsors use an optimal dose identified instead of a fixed standard dose. Could you please clarify if this is ITP specific requirement and what the rationales are?	Comment: The "standard" dose is very flexible (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). It is not clear what is meant by optimal in "*Quite often, sponsors use an optimal dose*"
Line 253	3	Comment: Proposed change (if any): full stop missing	Accepted.
Line 259 - 260	10	Could you please clarify which of the listed efficacy parameters is suggested as the primary efficacy	Not accepted. The ITP GL does not specifically recommend a primary

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		endpoint and at what time point?	endpoint. In the latest procedures with ITP indication there were different primary endpoints. See also SmPC section 5.1 of approved ITP products, e.g. Doptelet (avatrombopag), Tavlesse, Eltrombopag, Romiplostim.
Line 262	3	Comment: Proposed change (if any): should be >30x10*9/l	Accepted.
Lines 262-263	5	Comment: there could be times where the response criteria may need to be amended -notably in patients who need to undergo an invasive procedure and start with a platelet count under 25, i.e. "patients with R: platelet count >30 x 109/L" could be altered. In that situation, doubling of the platelet count might not be adequate for an invasive procedure Proposed change (if any): "patients with R: platelet count >30 x 109/L or, platelet count adequate for planned invasive procedure"	Not accepted. Patients who need to undergo a planned invasive procedure are normally not included in this short clinical trial setting. In an emergency operation they would be regarded as protocol deviations and obviously other rules of treatment would apply
Line 264	3	Comment: Proposed change (if any): should be >100x10*9/l	Accepted.
Line 266	3	Comment: Proposed change (if any): should be <30x10*9/l	Accepted.
Line 266-267	5	Comment: In the suggested response definition for a study in ITP, it is recommended that the definition of NR be further clarified. Specifically, would subjects who had platelet elevation above 30x109/L and	Accepted.

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		doubling from baseline for a few days (but less than 7) and then fell again to below 30x109/L be defined as NR? **Should a non-responder simply be described as someone who never achieves a response.** Proposed change (if any): "patients with NR: patients who did not achieve the stated response criteria would be defined as NR."	
Line 268	3	Proposed change: should be below 100x10*9/l	Accepted.
Line 269	3	Proposed change: should be below 30x10*9/l	Accepted.
Line 278	2	Comment: In the paragraph "5.3.4 Measles post-exposure prophylaxis": If possible, delete "lot 176", and replace with "CBER Reference Standard" as lot 176 will likely be replaced by another lot in the future. Proposed change: Please consider replacing "lot 176" with "CBER Reference Standard"	Accepted. Added as CBER Standard.
Line 278	4	Comment: a short justification, e.g. with reference to the publications or data sources consulted, should be for the addition to the product specification of *"0.36 x CBER Standard lot 176 anti-measles antibody titre threshold"*	Accepted. Added reference
Lines 284-286	1	Comment: Myasthenia Gravis responds well to IVIG in patients with myasthenic crisis. I propose to add this	Not accepted. See comment above.

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		indication. Proposed change (if any): then an extrapolation to GBS, Kawasaki disease, MMN, CIDP and Myasthenic crisis might be possible	
Line 304	10	This section cites that "safety signals should be compared with data and frequencies described in the literature". It is suggested to expand this wording to include other data sources, including data from electronic health care records and registries that may inform on IVIG product-event pairs.	Not accepted. Under the General Data Protection Regulation (GDPR) it might prove difficult in terms access to registries and e-health records etc. to obtain these data. We would prefer to keep the wording as it is.
Line 305	6	Proposed change: patient instead of subject	Accepted.
308-310	10	Comment: This section highlights monitoring of short-term tolerance and infusional AEs. For completeness, it is suggested to expand this section to highlight consideration of delayed reactions (i.e., thromboembolic events, hematologic complications and renal complications, as well as late reactions (dermatologic reactions, effects on efficacy, and infectious risks).	Partly accepted (added reference to the coreSmPC).
Line 312	10	As the risk of adverse reactions generally correlates with the dose of IVIG within each course and the rate of infusion, it is suggested to rephrase the statement to "AEs should be evaluated with regard with regard to	Accepted.

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		dose of the IVIG course and infusion rate".	
323	10	Comment: • temperature should be corrected from "70°C" to "-70°C"	Accepted.
Line 343	2	Comment: Section 5.6.2. 'Other transmissible agents'. Please consider including a sentence stating that "no transmissions of prions have been reported with use of IVIG products". Proposed change: Please see comment above.	Accepted.
Line 361	3	Proposed change: should be comparable	Accepted.
Lines 407	2	Comment: There is a line shift. 'Multifocal motor neuropathy' should be in line 407. Proposed change: Please see comment above.	Accepted.
Lines 408-409	2	Comment: There is a line shift. PID Primary Immunodeficiencies should be in line 408	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		and SID Secondary immunodeficiency should be in line 409 Proposed change: Please see comment above.	