16 December 2021
EMA/30450/2021
Blood Products Working Party (BPWP)

Overview of comments received on Guideline on core SmPC for human normal immunoglobulin for intravenous administration (IVIg) (EMA/CHMP/BPWP/94038/2007 Rev. 6)

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

Stakeholder no.	Name of organisation or individual
1	Plasma Protein Therapeutics Association (PPTA)
2	Netherlands Medicines Evaluation Board (MEB)
3	International Plasma and Fractionation Association (IPFA)
4	UCB Pharma

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1. General comments – overview

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
1	For the span or range of numbers a dash should be used instead of hyphen (e.g., 0–18 years) throughout the text. In the table reported under the paragraph "4.2 Posology and method of administration", the "indication/dose/frequency of injections" for measles seems to be missing. Throughout the text: According to the QRD recommendation on stylistic matters for English text abbreviation for litre should be written in capital letters: L, mL etc. General comment but especially for section 4.2: For some indications number of days, weeks or month are given in letters, whereas for others they are given in digits. This should also be aligned throughout the document and given in digits. Furthermore, alignment is needed for the use X to Y or X-Y days/weeks/months. For example: (line 204): 3–6 months (line 206 and 216): 3–4 weeks (line 242:) given on day 1	Accepted.
2	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	Partly accepted.

Stakeholder no. *(See cover page)*	General comment (if any)	Outcome (if applicable)
	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 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	….in whom active immunisation is contraindicated or is not advised. References added, also for GL
3	IPFA acknowledges the inclusion of the Measles indication and has no general comments.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
10-11	1	Comment: Keywords: "Measles post-exposure prophylaxis" is missing. Proposed change: Add the keyword "Measles post-exposure prophylaxis".	Accepted.
147	1	Comment: <Minimum **content** anti-measles IgG is {x} IU/ml> This is not content but a level, activity or titer. Proposed change (if any): Consider rewording to '<Minimum **level** anti-measles IgG is {x}…>'	Accepted.
175-176	1	Comment: The age range is missing, accoridng to QRD template considered, as done for the other existing indications. What is the recommendation for paediatric use? What is the recommendation for paediatric patients aged 0-2y, 2-11y, 12-18y, and how is this considered for	Accepted: <u>for susceptible adults, and children and adolescents (0-18 years) in whom…..</u> Patients with these underlying disorders would be treated with IVIG in any case.

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		paediatric patients with another underlying disease, e.g. CIDP, Kawasaki, PID etc.? Proposed change: Please add an age range.	
175–176	1	Comment: Clarification needed: Should the indication "measles post-exposure prophylaxis" be written in line with Section 4.2 (<measles post-exposure prophylaxis>) (line 223)? Proposed change: 4.1 and 4.2: <Measles post-exposure prophylaxis for susceptible persons in whom active immunisation is contraindicated.>	Not accepted. In 4.2. it is not necessary to repeat the entire wording of the indication – this is also not done for PID or SID.
176	1	Comment: Clarification needed: The term "contraindicated" might be confusing. Are patients with e.g., severe PID where vaccination was just ineffective and a re-vaccination is not further recommended/useful, not in scope of this indication? Proposed change: Please clarify, as per comment above.	Partly accepted. Reworded indication: < Measles pre-/post exposure prophylaxis for susceptible adults, children and adolescents (0-18 years) in whom active immunisation is contraindicated or not advised.>

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
176	2	Comment: 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. Proposed change: Contraindicated or not possible	See comment above.
177	1	Comment: Following change is suggested to distinguish from and avoid confusions with subcutaneous or intramuscular immunoglobulin. (e.g. their dosing regimens) Proposed change (if any): Consideration should also be given to official recommendations **on intravenous human immunoglobulin use** in measles post-exposure	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		prophylaxis	
177	2	Comment: The recommendation to take national recommendations into consideration can adequately accommodate national positions on active immunization. Proposed change (if any): Consideration should also be given to official recommendations on measles post exposure prophylaxis and active immunisation.	Accepted.
189, 278	1	Comment: 4.1 Indication includes sub-headers for replacement therapy and immunomodulation. However, Line 189 only refers to replacement therapy. Please consider adding another sub-header "Immunomodulation" to section 4.2, as it is also given in the dosage table (line 278) and in section 4.1. Proposed change: 'Replacement and immunomodulation therapy (OR simply: "IVIg therapy") should be initiated and monitored under the supervision of a physician experienced in the treatment of immunodeficiency'.	Partly accepted: IVIg therapy should be initiated and monitored under the supervision of a physician experienced in the treatment of immune system disorders.
215	1	Comment:	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		The line should follow the wording of section 4.1 and line 202. Proposed change: 'Replacement therapy in secondary immunodeficiencies (as defined in 4.1).'	
223-233	2	Comment: It is suggested that a short justification, e.g. with reference to the publications or data sources consulted, should be given for the target serum level of measles antibodies of >240 mIU/mL	Accepted. Added: This *provides a safety margin double that of the WHO protective titer* https://www.who.int/immunization/monitoring_surveillance/burden/laboratory/Chapter_9.pdf?ua=1
228-235	1	Comment: The following paragraph is a repetition of the next paragraph (233-235): 'If a susceptible patient has been exposed to measles, a dose of 400 mg/kg given as soon as possible and within 6 days of exposure should provide a serum level > 240 mIU/mL of measles antibodies for at least two weeks. Serum levels should be checked after 2 weeks and documented. A further dose of 400 mg/kg may be necessary to maintain the serum level > 240 mIU/mL.	Partly accepted. AS PID/SID will most likely be receiving regular doses of IVIG it is deemed to be clearer if these 2 patient groups are kept separate. The pre-exposure prophylaxis was put in a separate paragraph.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		If a PID/SID patient has been exposed to measles and regularly receives IVIG infusions, it may be prudent to administer an extra dose of IVIG as soon as possible and within 6 days of exposure. A dose of 400 mg/kg should provide a serum level > 240 mIU/mL of measles antibodies for at least two weeks.' Proposed change: Consider combining both paragraphs and shortening the entire section.	
228-238	1	Comment: The dose is given in mg/kg, for all other indications it is given in g/kg. This should be aligned throughout the text. Proposed change: See comment.	Accepted.
236-237	1	Comment: Clarification needed: The term "dose" in line 237 is confusing. It is not clear to what dose the term refers to – is this the PID "maintenance dose" for instance, or the "measles single dose"? This needs adequate wording to avoid overdosing in PID patients switching to therapy with maintenance doses to of 530mg/kg, based on the current core	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		SmPC language. Proposed change: Please clarify as per comment above.	
236-238	1	Comment: Consider adding a new paragraph because the sentence mentions 'pre-exposure prophylaxis' Proposed change: Please see comment above, considering adding a new paragraph.	Accepted.
237	1	Comment: ">" character missing in sentence '240 mIU/mL' (please see line 235). Proposed change: Please add ">" prior to '240 mIU/mL' for consistency or justify, if not added.	Accepted.
243	1	Comment: The wording should be aligned with line 248. Proposed change: (line 243:) 0.4g/kg/day given for 2–5 days	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
243-245	1	Comment: The sentence is in correctly separated across the lines. **'...-0.4 g/kg given daily for two to five** **days. The treatment can be repeated if** **relapse occurs.'** Proposed change (if any): Correction needed as per comment above.	Accepted.
248-249	1	Comment: Please add a line between the two sentences below: **'...0.4 g/kg/day over 5 days (possible repeat of dosing in case of relapse).** **Kawasaki Disease'** Proposed change: **'...0.4 g/kg/day over 5 days (possible repeat of dosing in case of relapse).** **Kawasaki Disease'**	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
249	1	Comment: Clarification required: Does the Kawasaki indication include the Kawasaki-like Multisystem Inflammatory Syndrome too? Proposed change: Please clarify, as per comment above.	Comment: It is acknowledged that many MIS patients are treated with IVIGs. However, Kawasaki-like MIS temporally associated with SARS-CoV-2 infection has patient characteristics that differ from those of classic Kawasaki disease. Further studies are needed to optimise treatment strategies. Thus, it is suggested to currently keep this wording. *Management of Multisystem Inflammatory Syndrome in Children Associated With COVID-19: A Survey From the International Kawasaki Disease Registry* https://www.sciencedirect.com/science/article/pii/S2589790X20301372 "There is variation in management of MIS-C patients, with suboptimal evidence to assess superiority of the various treatments; evidence-based gaps in knowledge should be addressed through worldwide collaboration to optimize treatment strategies." *Emerging Evidence on Multisystem Inflammatory Syndrome in Children Associated with SARS-CoV-2 Infection: a Systematic Review with Meta-analysis* https://link.springer.com/article/10.1007/s42399-020-00690-6

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			From the NIH treatment guidelines 7/2020 https://www.covid19treatmentguidelines.nih.gov/immunomodulators/ivig---non-sars-cov-2/: **Considerations in Children** IVIG has been widely used in children for the treatment of a number of conditions. including Kawasaki disease, and is generally safe.4 IVIG has been used in pediatric patients with COVID-19 and multiorgan inflammatory syndrome in children (MIS-C), especially those with a Kawasaki disease-like presentation, but the efficacy of IVIG in the management of MIS-C is still under investigation.
256	1	Comment: The wording should be in line with the starting dose to avoid confusion. Proposed change: '1 g/kg **divided** over 1-2 consecutive days every 3 weeks'.	Accepted.
264	1	Comment: See above, as for line 256 Proposed change:	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Starting dose: 2 g/kg **divided/ given** over 2-5 consecutive days.	
278–279	1	Comment: The table with dosage recommendations does not include "measles post-exposure prophylaxis". Proposed change: Please add "measles post-exposure prophylaxis" and appropriate posology to the table.	Accepted.
278	1	Comment: Table, column header: "frequency of injections" should be amended to "frequency of infusions" Proposed change: Change to "**frequency of infusions**"	Accepted.
278	1	Comment: Table: Immunomodulation is underlined and followed by ":" Replacement therapy not. With respect to these sub-headers in the dosage table it should be consider how to present "Measles post-exposure prophylaxis" in this table (include a sub header? –Should be consistent in 4.1 and 4.2).	Accepted.
278	1	Comment:	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		<table><tr><td>Primary immunodeficiency syndromes</td><td>Starting dose: 0.4 - 0.8 g/kg Maintenance dose: 0.2 - 0.8 g/kg</td><td>every 3 - 4 weeks</td></tr></table> Within the table –indication: Primary immunodeficiency syndromes. Frequency of injections should be aligned with maintenance dose instead of the starting dose. Proposed change: Pease see comment above.	
278	1	Comment: The table for CIDP should be corrected (please delete dividing line): <table><tr><td>Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)</td><td>Starting dose: 2 g/kg</td><td>in divided doses over 2-5 days</td></tr></table> Proposed change: Please see comment above.	Accepted.
292	1	Comment: A space is missing after the word “section” Proposed change:	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Please add a space between "section" and "4.4".	
296	1	Comment: The EDQM Standard term should be used to describe intravenous use. Proposed change: Please change from 'For intravenous use' to '**Intravenous use**'.	Accepted.
321	1	Comment: '…are not sensitive to human normal immunoglobulin by initially **injecting** the product slowly…' Proposed change: Consider rephrasing to '…are not sensitive to human normal immunoglobulin by initially **administering** the product slowly…'	Accepted.
326 -328	4	Comment: This section cites that "patients naive to human normal immunoglobulin, patients switched from an alternative IVIg product or when there has been a long interval since the previous infusion should be monitored at the hospital during the first infusion and for the first hour after the first infusion, in order to detect potential	Partly accepted. In particular, patients naive to human normal immunoglobulin, patients switched from an alternative IVIg product or when there has been a long interval since the previous infusion should be monitored during the first infusion and for the first hour after the first infusion in a controlled healthcare setting in order to detect potential adverse signs

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		adverse signs." As healthcare delivery setting terminology may vary, it is suggested to consider rewording to state that the first infusion should always be administered in a controlled healthcare setting where emergency treatment can be administered immediately should problems occur.	and where emergency treatment can be administered immediately should problems occur.
331	1	Comment: "…the initiation of the infusion of IVIg" Proposed change: Please consider rephrasing to '…initiation of IVIg infusion'	Accepted.
348	1	Comment: Patients receive IgG in order to treat and prevent recurring infections. Therefore, the statement "in patients with an untreated infection or underlying …" is misleading. Proposed change: Consider changing to "in patients with an **active** infection or underlying ….".	Accepted.
391	1	Comment: Meaning of AMS is given in the title of the paragraph,	Accepted.

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		hence this can be abbreviated in line 391 Proposed change: Consider rephrasing to 'AMS has been reported…'	
392	1	Comment: Consider adding abbreviation of Cerebrospinal fluid, as the abbreviation is also used in line 398. Proposed change: 'Cerebrospinal fluid (CSF) studies…'	Accepted.
407	1	Comment: Please correct: 'red blood cell**s** (RBC) sequestration' to 'red blood cell (RBC)…' Proposed change: Please see comment above.	Accepted.
420	1	Comment: 'Symptoms of TRALI typically develop during or within 6 hours of a transfusion'. Add missing word. Proposed change:	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		'Symptoms of TRALI typically develop during or within 6 hours **after** a transfusion.'	
456-458	1	Comment: Line shift Proposed change: Correction needed.	Accepted.
469	1	Comment: In section 4.6 there are separate sub-headers for pregnancy, breast-feeding and fertility, however within the paragraph "pregnancy" also information for breast feeding mothers is given. This should be shifted to the respective sub header: "The safety of this medicinal product for use in human pregnancy has not been established in controlled clinical trials and therefore should only be given with caution to pregnant women and **breast-feeding mothers**." Or this information should be shifted above sub-header for pregnancy.	Accepted.
475-478	3	Comment: The wording related to breast feeding is not in accordance with the QRD template. Proposed change (if any): Breast-feeding Immunoglobulins are excreted into human milk, but at therapeutic doses no ~~negative~~ effects on the breastfed	Not agreed. Wording to be maintained. One article indicates transferral of IgG in breast milk of mothers receiving IVIG with e.g strong inhibition of enteropathogenic E. coli adhesion *in vitro*. https://pubmed.ncbi.nlm.nih.gov/19220771/

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		newborns/infants are anticipated. {Invented name} can be used during breast-feeding. Immunoglobulins are excreted into human milk. No negative effects on the breastfed newborns/infants are anticipated.	Overview: https://www.drugs.com/breastfeeding/immune-globulin.html
541-542	1	Comment: The following statement does not include infants: 'Overdose may lead to fluid overload and hyperviscosity, particularly in patients at risk, including elderly patients or patients with cardiac or renal impairment.' Proposed change: The statement should include infants. 'Overdose may lead to fluid overload and hyperviscosity, particularly in patients at risk, including **infants**, elderly patients or patients with cardiac or renal impairment.'	Accepted.
554-555	1	Comment: Consider aligning the Core SmPC text with the European pharmacopoeia for IVIg products, reporting the wording "1000 donors" instead of "1000 donations" on section 5.1 of Core SmPC.	Accepted.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: 'Human normal immunoglobulin contains the IgG antibodies present in the normal population. It is usually prepared from pooled plasma from not fewer than 1000 donors.'	