23 July 2015
EMA/CHMP/BPWP/356919/2013
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on ' Guideline on clinical investigation of human normal immunoglobulin for subcutaneous and/or intramuscular administration SCIg/IMIg' (EMA/CHMP/BPWP/410415/2011 rev 1)

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

Stakeholder no.	Name of organisation or individual
1	IPFA
2	IPOPI

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	With regard to the previous guideline, the number of patients has been increased and the follow-up time is longer in this new guideline. This is something that is also found in other revised guidelines (ref. Mannucci paper)	The guideline is revised to be consistent where applicable with the updated guideline for human normal immunoglobulin for intravenous administration (EMA/CHMP/BPWP/94033/2007 current version). See also A. Hilger, C. Arras-Reiter, B. Keller-Stanislawski *et al.* (2013), Comment on: Mannucci, P. M. Evolution of the European guidelines for the clinical development of factor VIII products. **Haemophilia**, 19:349-350. doi: 10.1111/hae.12151

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 94 and 99	1	Comment: Are IMIgs ruled out for replacement therapy? Proposed change (if any): Line 94: Remove '(SCIg)' from line 94 or replace with '(SCIg/IMIg)'. Line 99: same as for line 94	Not accepted. Example: DE GL ***S3-Leitlinie*** ***„Therapie primärer Antikörpermangelerkrankungen"*** *AWMF-Register-Nr. 027/052, September 2012:* **Intramuscular administration of polyvalent immunoglobulin is no longer recommended** In the introduction it is stated that: Although IgG replacement therapy was initially administered intramuscularly, this route of administration can now be considered outdated for replacement therapy as the required doses to achieve adequate trough levels cannot be administered safely or without extreme discomfort for the patient.
Line 99 and 100	1	Comment: replacement therapy is considered an indication for SCIgs only in patients where IV cannot be used Proposed change (if any): "replacement therapy is therefore considered an indication for SCIgs when IVIg are contra-indicated in the following situations. And see comment above.	Not accepted SCIG is not just to be used when IVIGs are contraindicated

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102	2	Comment: SCIg is now routinely used in the treatment of SCID infants pre and post HSCT. Proposed change (if any): Primary immunodeficiency syndromes with impaired antibody production including in children with severe PIDs such as Severe Combined Immunodeficiency (SCID) requiring Hematopoietic Stem Cell Transplantation (HSCT)	Partly accepted See CoreSmPC revised wording: Hypogammaglobulinaemia in patients pre- and post-allogeneic haematopoietic stem cell transplantation (HSCT)
Lines 140-141	1	Comment: Trough levels are supposed to be assessed before the next infusion, SCIg are often administered on a ½-weekly basis. Proposed change (if any): Replace …'assessed on a monthly basis'… With …'assessed prior to the next infusion at a relevant rate and duration, for example before each infusion for 5 infusions or on a monthly basis '… Replace …', starting after 4 months'… With …,' starting after 4-6 infusions'…	Not accepted The aim was to obtain corresponding trough data to IVIGs - thus the monthly basis (notwithstanding the differences between the administration routes), rather than measuring before each weekly infusion, also beginning after 4 months rather than after 4-6 infusions (= 4-6 weeks).
Lines 138 - 151	1	Comment: The sentence 150-151 mentions that a PK study in children is not deemed necessary, due to extrapolation of data. This is in conflict with part 1 of the paragraph 'PK parameters' (IgG trough levels), in which is described that children/adolescents should be	Accepted

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		included Proposed change (if any): Change this paragraph, either do not require to include children in the PK study altogether or Change Lines 150-151 e.g.: Replace …'immunoglobulins, PK in adults can be'… With …'a separate paediatric PK study is not deemed necessary and children included should only be assessed for through levels and not for other PK parameters including area under the curve, Cmax, and Tmax'	
144-145	1	Comment: In our knowledge, there are no publications on SCIg pharmacokinetics in naïve patients Proposed change: For Group C, a descriptive comparison to published literature (if any) is requested	Partially accepted As the use of SCIG is spreading to treat more PID (and possibly other patients) and more studies are being performed, more data will become available also for PK in naïve patients. See e.g. Hyqvia Public AR http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002491/WC500143854.pdf
220-221	1	Comment: The analysis of AEs that begin during or within 72 hours after an infusion is relevant with IVIg	Partially accepted.

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		but may be pointless with SCIg for the following reasons : It is now well known that IgG concentration in blood is far more stable when immunoglobulins are administered subcutaneously every week than when immunoglobulins are administered intravenously every 3 to 4 weeks. Therefore, “during or within 72 hours after an infusion” is a period of time with high risk of adverse reactions when intravenous Ig have been administered, but risks are not particularly high when subcutaneous immunoglobulin have been administered (according to Berger 2001 publication, blood concentration of SCIg peaks at a mean of 61.7 hours after subcutaneous infusion, with ranges from 11 to 175 hours). This means that AR would rather occur at the third day (with a wide range), day of the concentration peak, if any. Immediate infusional reactions over 3 days with IVIg infusion every 3-4 weeks are relevant. The same observational period cannot be applied for a weekly SCIg infusion. The concept of infusional AE is not relevant in such a short infusion interval and such flat and variable concentration peak. It would rather be relevant to observe all events, not only infusional events. Proposed change: To delete the following sentence “All AEs that begin during or within 72 hours after an	The issue with Cmax and its wide range is a valid one. Rewording: Safety evaluation should include monitoring of short term and local tolerance (blood pressure, heart rate, temperature, and monitoring of other adverse events, skin reactions) at repeated intervals following the infusion of the new product. Local reactions should be evaluated with regard to the anatomical localisation, infusion rate and infused volume per site of injection.

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		infusion should be classified and analysed as infusional AEs"	
221 - 222	1	Comment: The evaluation of AEs with regard to the infusion rates is pertinent for intravenous immunoglobulin but not for subcutaneous immunoglobulins, for the following reasons: • More than 1 injection site may be involved during a subcutaneous infusion, and consequently more than one flow rate may be used. • Systemic adverse reactions are very infrequent with subcutaneous Ig. • Subcutaneous infusion flow rate is unlikely to influence systemic adverse reactions due to the time lapse between administration in the subcutaneous tissue and the inflow of product in blood. Infusion flow rate is more likely to influence the rate of local adverse reactions. Proposed change (if any) Replace: "AEs should be evaluated with regard to the infusion rates." with: "Local reactions should be evaluated with regard to the anatomical localisation, infusion rate and infused volume per site of injection."	Accepted. See rewording above.
225	2	Comment: Post-marketing safety data collection in children should not only be proposed but required	Accepted

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change (if any): Post-marketing safety data collection in children should be ~~proposed~~ required in the risk management plan.	