26 February 2015
EMA/CHMP/BPWP/356950/2013
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Guideline on core SmPC for human normal immunoglobulin for subcutaneous and intramuscular administration' (EMA/CHMP/BPWP/143744/2011 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	University of Oxford - Professor Helen Chapel
2	International Patient Organisation for Primary Immunodeficiencies - IPOPI

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1. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
Line 61	1	comment: <Antibodies to Hepatitis A at least (x) IU/ml> - since vaccines to hep A are widely available, this requirement/sentence is out of date. If intended as a surrogate for protective antibodies for PIDs, it is not the correct antibody to measure Proposed change (if any): omit	Not accepted The requirement of an anti-Hepatitis A antibody content is linked to the indication (see below)
Line 92	1	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 (see section 4.4) including in children with severe PIDs such as Severe Combined Immunodeficiency (SCID) requiring Hematopoietic Stem Cell Transplantation (HSCT)	Partially accepted. Revised text: Hypogammaglobulinaemia in patients pre- and post-allogeneic haematopoietic stem cell transplantation (HSCT)
Line 92	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	Same comment as above.

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		antibody production (see section 4.4) including in children with severe PIDs such as Severe Combined Immunodeficiency (SCID) requiring Hematopoietic Stem Cell Transplantation (HSCT)	
Line 95	1	Comment: Hypogammaglobulinaemia and recurrent bacterial infections in plateau phase multiple myeloma patients who have failed to respond to pneumococcal immunisation. Haematologists do not use the phrase “plateau” anymore and since most patients who respond well to chemotherapy get autologous transplants now – so please check Proposed change (if any) Suggest omit or change to Hypogammaglobulinaemia and recurrent bacterial infections in ~~plateau phase~~ multiple myeloma patients ~~who have failed to respond to pneumococcal immunisation~~.	Accepted modification of text
Line 100	1	Comment <- Hepatitis A prophylaxis in travellers who present less than 2 weeks before possible exposure, preferably in combination with vaccination. Change <- Hepatitis A prophylaxis in very rare travellers who present less than 2 weeks before ~~possible~~ likely	Partially accepted The rate of non-vaccinated travellers is not known and may differ from country to country. Very rare would imply 1: 10,000 In a recent review (Feb 2013) http://www.uptodate.com/contents/hepatitis-a-virus-vaccination-and-postexposure-prophylaxis#H20) the following is stated *With the vaccine, seropositivity by RIA was seen in 73% at*

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		exposure, preferably in combination with vaccination.	*week 2, 100% at week 5, and 100% at week 24. The comparable values for seropositivity after IG were 100% at week 1, 10% at week 12, and 0% at week 20.* The recommendation of the Advisory Committee on Immunization Practices is as follows: *Individuals with recent exposure to HAV who have not previously received HAV vaccine should be administered a single dose of single-antigen HAV vaccine or immune globulin (IG) (0.02 mL/kg) as soon as possible. For healthy individuals aged 12 months to 40 years, single-antigen hepatitis A vaccine at the age-appropriate dose is preferred. For children aged <12 months, immunocompromised individuals, patients with chronic liver disease, and individuals for whom vaccine is contraindicated, IG should be used.* In a preparation containing 100 IU/ml the suggested dose of 0.02ml/kg would offer 1 month protection, for a 3 month protection the currently suggested dose of 0.17 ml/kg as given in the 1993 article by H.L. Zaaijer was deemed to be adequate. TABLE III. Calculated Immunoglobulin Dosage (ml/kg) for Preparations With Different Anti-HAV Contents Based on a Minimum Protective Level of 10 mIU/ml and a Half-Life of Immunoglobulin of 21 Days (Dosage for Persons of 40 and 80 kg) Preparation (IU/ml) / Protection: 1 month; 2 months; 3 months; 4 months 100: 0.02 (1 ml, 2 ml); 0.06 (2.5 ml, 5 ml); 0.17 (6.5 ml, 13 ml); 0.45 (18 ml, 36 ml) 150: 0.02 (0.5 ml, 1 ml); 0.04 (1.5 ml, 3 ml); 0.11 (4.5 ml, 9 ml); 0.30 (12 ml, 24 ml) 200: 0.01 (0.5 ml, 1 ml); 0.03 (1 ml, 2.5 ml); 0.08 (3.5 ml, 6.5 ml); 0.23 (9 ml, 18 ml) 250: 0.01 (0.5 ml, 0.5 ml); 0.02 (1 ml, 2 ml); 0.07 (2.5 ml, 5 ml); 0.18 (7 ml, 14.5 ml) 300: 0.01 (0.5 ml, 0.5 ml); 0.02 (1 ml, 1.5 ml); 0.06 (2 ml, 4.5 ml); 0.15 (6 ml, 12 ml) This is more than is advised by the CDC (http://www.cdc.gov/hepatitis/hav/havfaq.htm) *single dose of IG (0.02 mL/kg), which provides effective protection against Hepatitis A virus infection for up to 3 months. Travelers whose travel period exceeds 2 months*

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			should be administered IG at 0.06 mL/kg; administration must be repeated if the travel period exceeds 5 months. However, as in the CDC recommendation specific products and their potency are not mentioned, it may be preferable to keep the suggested dosing.
Line 105	1	Comment Hepatitis A prophylaxis in persons exposed less than 2 weeks previously.> Change Hepatitis A prophylaxis in non-immunised individuals ~~persons~~ know to have been exposed less than 2 weeks previously.>	Accepted (Changed to unvaccinated individuals….)
Line 129	1	Comment The dose regimen should achieve a trough level of IgG (measured before the next infusion) of at least 5 to 6 g/l. Change The dose regimen should achieve a trough level of IgG (measured before the next infusion) well within the normal range of serum IgG for age	Partially accepted. It is considered advisable to keep a concrete figure for a lower limit. Amended text: The dose regimen should achieve a trough level of IgG (measured before the next infusion) of at least 5 to 6 g/l and aim to be within the reference interval of serum IgG for age.
Line 130	1	Comment A loading dose of at least 0.2 to 0.5 g/kg ({XX} to {YY} ml/kg) body weight may be required. Change	Not accepted It is felt that in a coreSPC concrete figures are helpful and the loading dose should therefore be retained. The reference to the intravenous loading dose may possibly

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		A loading dose ~~of at least 0.2 to 0.5 g/kg ({XX} to {YY} ml/kg) body weight may be required: this~~ is usually given IV since large doses may be needed to increase IgG levels speedily in those with primary immunodeficiencies.	give rise to confusion and misuse of the SCIG product
Line 130	1	Comment A loading dose of at least 0.2 to 0.5 g/kg ({XX} to {YY} ml/kg) body weight Change This is very small for a loading dose when maintenance is 0.4-0.8 g/Kg- perhaps you mean 2 g/Kg?	Comment In the current product specific SPC for SCIGs the loading dose 0.2 to 0.5 g/kg is given for the SCIG (not for an IVIG) – the maintenance dose of 0.4 to 0.8 g/kg is the monthly cumulative dose
Line 137	1	Comment the rate of infection, it may be necessary to increase the dose and aim for higher trough levels. Change the rate of serious or moderate bacterial infection, it may be necessary to increase the dose and aim for higher trough levels in individual patients.	Not accepted Although it is obvious that the aim is to reduce SBIs (which are well defined), it is not quite clear how to define moderate infections. The broader (original) wording would accommodate both.
Line 167/8	1	Comment The infusion site should be changed every 5-15 ml. Doses over 15 ml should be divided Change The amount of product infused into a particular site varies. In infants and children, infusion site may be changed every 5-15 ml. In adults doses over 30 ml may be divided according to patient preference	Accepted
Line 169	1	Comment The recommended maximum number of infusion sites is {X}.	Accepted

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		Change There is no limit to the number of infusion sites	
Line 183	1	Comment If {(Invented) name} is accidentally administered into a blood vessel patients could develop shock. Change Add " the infuser should check that the needle is not situated in a vein"	Comment In a recent Variation Procedure with a subcutaneous product the company had been asked to add to the PIL that the plunger of the syringe should be pulled to check for the presence of blood. However in their response they quoted the NHS Best Practice Guide (McAskill and Goodhand 2007) for sc injections: *It is not necessary to draw back on the plunger to ensure that the needle is not in the vein as it is unlikely that a blood vessel will be pierced.* This was considered acceptable
Line 199	1	Comment should be switched to {(Invented) name} change The question of IgA abs is still very controversial – since all products are now low in IgA – I suggest that you omit this part of the sentence	(L 201) Not accepted Products vary considerably in IgA content
Line 205	1	Comment are not sensitive to human normal immunoglobulin - this is very woolly change omit	Accepted
Line 220	1	Comment …..and pulmonary embolism have been associated with the use of immunoglobulins. This paragraph from line 217 is not really relevant to SCIg at all – SCIg takes 3-4 days to reach the	Not accepted. Although initially TEEs were thought to occur only with IVIGs, TEEs did occur with Vivaglobin. Factor XIa and not the high influx of protein in the vein was deemed to be the culprit. With the changing of the monographs (both IVIG and SCIG) to

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		circulation and the doses given are much smaller than those related to thromboembolism. Change ……and pulmonary embolism have been associated with the use of immunoglobulins, given intravenously or in large doses. Patients should be sufficiently hydrated before use of any therapeutic immunoglobulins and caution exercised in patients with preexisting risk factors for thrombotic events (such as advanced age and patients with diseases which increase blood viscosity).	reduce the procoagulant activity, this adverse event will hopefully diminish – but it would be premature to delete or change this text.
Line 235	1	Comment Excellent addition	
Line 339	1	You could add the thromboembolic bit here in overdosing if you wanted to – but it would need to be a big overdose!	See above.