15 September 2016
EMA/CHMP/BPWP/379278/2016
Committee for Medicinal Products for Human Use

Overview of comments received on 'Draft Guideline on the core SmPC for human Anti-D immunoglobulin for intravenous use' (EMA/CHMP/BPWP/319619/2005 Rev. 2)

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

Stakeholder no.	Name of organisation or individual
1	International Plasma Fractionation Association: IPFA, ref. IP-16-092

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1. General comments

Stakeholder number	General comment	Outcome
1	IPFA welcomes this Core SPC for Intravenous anti-D products.	

2. Specific comments on text

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Line 19	1	Comment: In our opinion the statement in these lines is contradicting. Since thromboembolic events (TEEs) with anti-D immunoglobulins have not been observed with products intended for intramuscular use special warnings are not necessary and are not applicable for this core SmPC. Especially since anti-D immunoglobulins have been used for years (> 50 years), also in patients with high risk of thrombosis, without any reports of TEEs. In the systematic review of McBain et al. two clinical trials were included (with over 4500 woman) and no adverse effects related to anti-D treatment were reported.[1] Moreover, in 2011 the UK Royal College of Obstetricians and Gynaecologists noted that: "There is no evidence to suggest that routine antenatal anti-D immunization prevention (RAADP) is associated with adverse events that are of consequence for the mother or baby, other than the possibility of bloodborne infection, and procedures are in place to minimize these risks and to inactivate viruses''.[2] Although anti-D immunoglobulin has been produced by IPFA member Organisations since the 1960s and has been registered since, thousands of patients have been treated with our products and to date we no reports of TEEs has been received. In 2011, cases of thromboembolic events, including strokes and pulmonary embolism were seen following treatment with a subcutaneous immunoglobulin, (SCIg) Vivaglobin. Although thromboembolic events are seen in relation to intravenous immunoglobulins (IVIgs), they had not previously been linked with SCIgs due to the retarded absorption.[3] Following these events the European Medicines Agency included TEE warnings in the summary of product characteristics (core SPC) of subcutaneous immunoglobulins .[4] However, also the TEE risk in relation to IVIgs is still under debate especially since Ammann et al. concluded in their recent meta-analysis that they did not find evidence of elevated TEE risk attributable to IVIg.[5] Moreover, the risk of thromboembolic events is of particular concern when high-dose intravenous immunoglobulin	Not accepted. This comment seems more related to anti-D immunoglobulin for intramuscular use than anti-D immunoglobulin for intravenous. However please see also the outcome of the *Overview of comments on draft core SPC anti D IM*.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		therapy (≥1 g/kg) is used and administered rapidly.[6,7] These high doses will never be reached with anti-D immunoglobulin, even in case of a foeto-maternal transfusion. Literature 1. McBain RD, Crowther CA, Middleton P. Anti-D administration in pregnancy for preventing Rhesus alloimmunisation. Cochrane Database Syst Rev. 2015 Sep 3;9:CD000020. 2. Royal College Obstetricians & Gynaecologists (RCOG): Green-top Guideline 22 The Use of Anti-D Immunoglobulin for Rhesus D Prophylaxis. "It should be noted that anti-D Ig does not protect against the development of other antibodies which can cause haemolytic disease of the newborn"; 2011:4. http://www.rcog.org.uk/womens-health/clinical-guidance/use-anti-dimmunoglobulin-rh-prophylaxis-green-top-22. 3. European Medicines Agency. Core SPC for human normal immunoglobulin for intravenous administration (IVIg) (CPMP/BPWG/859/95 rev. 2). Committee for Medicinal Products for Human Use. 2004. 1–8. Available at: http:// www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2010/01/WC500067337.pdf 4. European Medicines Agency Guideline on core SmPC for human normal immunoglobulin for subcutaneous and intramuscular administration. Committee for Medicinal Products for Human Use. 2012. 1–10. Available at:http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500130466. 5. Ammann EM, Haskins CB, Fillman KM, Ritter RL, Gu X, Winiecki SK, Carnahan RM, Torner JC, Fireman BH, Jones MP, Chrischilles EA. Intravenous immune globulin and thromboembolic adverse events: A systematic review and meta-analysis of RCTs. Am J Hematol. 2016 Mar 11. 6. Silvergleid AJ, Perez E, Intravenous immune globulin: Adverse effects, Uptodateonline article, last updated, Feb 23, 2016. http://www.uptodate.com/contents/intravenous-immune-globulin-	

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		adverseeffects?source=search_result&search=intravenous+immunoglobulin&selectedTitle=2%7E150 7. Caress JB, Hobson-Webb L, Passmore LV, Finkbiner AP, Cartwright MS. Case-control study of thromboembolic events associated with IV immunoglobulin. J Neurol. 2009;256(3):339. Proposed change (if any): Consider removing warnings on TEE-risk	
119-125	1	Comment: The structure of paragraph and sentence needs to be amended: ▹ *Antenatal prophylaxis.* According to general recommendations, currently administered doses range from 50 – 330 micrograms or 250 - 1650 IU. *Planned antenatal prop*hylaxis: Proposed change (if any): • *Antenatal prophylaxis.* According to general recommendations, currently administered doses range from … ▹ Planned antenatal prophylaxis: (no italic) … ▹ Antenatal prophylaxis following complications of pregnancy … • *Postnatal prophylaxis*	Accepted.
119-124	1	Comment: The half-life of anti-D antibodies is estimated to be 17 to 22 days[1]. Therefore the two main approaches of antenatal prophylaxes are a singles dose of 1500 international units (IU) at 28 weeks or 500 to 625 IU at 28 and 32 weeks[2,3]. This dosage protects against immunization after exposure to 1 ml of red blood cells or 2 ml of whole blood. It is extremely unlikely that the volume of antenatal transplacental haemorrhage would exceed 1 ml of foetal red blood[4]. Koelewijn et al. (2008)[5] showed in a Dutch nation-wide historical	Not accepted. Core SPC is intended to provide information to be included in the SPC of products authorized in several Countries with potential different national recommendations. For this reason the statement actually present in the core SPC is considered more appropriate.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		control study (with in total 20.700 pregnant woman) that RAADP of one single dose of 1000 IU of anti-D immunoglobulin in addition to one single postnatal dose of 1000 IU anti-D immunoglobulin halves the risk of anti-D immunization and subsequently severe haemolytic disease of the foetus or newborn and enhanced compliance over the two-dose protocol with the potential for reduced sensitization combining economic and manpower benefits[7]. Lee and Rawlinson found no benefit of a smaller dose of antenatal anti-D (250 IU)[6]. Proposed change (if any): We advise to change the antenatal dosing advice from 250-1650 to 500-1500 IU as recommended in current literature.[1,2,5] Moreover, the proposed text in the draft core SmPC on the single and the second dose is confusing. We propose to change this in the following: 1. Either a single dose of 1000-1500 IU at 28 - 30 weeks of gestation or two doses of 500-625 IU at 28 and 34 weeks. Literature 1. Bichler J, Schöndorfer G, Pabst G, Andresen I. Pharmacokinetics of anti-D IgG in pregnant RhD-negative women. BJOG. 2003 Jan;110(1):39-45. 2. McBain RD, Crowther CA, Middleton P. Anti-D administration in pregnancy for preventing Rhesus alloimmunisation. Cochrane Database Syst Rev. 2015 Sep 3;9:CD000020. 3. MacKenzie IZ, Roseman F, Findlay J, Thompson K,	

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Jackson E, Scott J, Reed M. The kinetics of routine antenatal prophylactic intramuscular injections of polyclonal anti-D immunoglobulin. BJOG. 2006 Jan;113(1):97-101. 4. Caress JB, Hobson-Webb L, Passmore LV, Finkbiner AP, Cartwright MS. Case-control study of thromboembolic events associated with IV immunoglobulin. J Neurol. 2009;256(3):339. 5. Koelewijn JM, de Haas M, Vrijkotte TG, Bonsel GJ, van der Schoot CE. One single dose of 200 microg of antenatal RhIG halves the risk of anti-D immunization and hemolytic disease of the fetus and newborn in the next pregnancy. Transfusion. 2008 Aug;48(8):1721-9. 6. Lee D, Rawlinson VI. Multicentre trial of antepartum low-dose anti-D immunoglobulin. Transfus Med. 1995 Mar;5(1):15-9. 7. MacKenzie IZ, Dutton S, Roseman F. Evidence to support the single-dose over the two-dose protocol for routine antenatal anti-D Rhesus prophylaxis: a prospective observational study. Eur J Obstet Gynecol Reprod Biol. 2011 Sep;158(1):42-6.	
160 -162 **4.2 Posology and method of administration** Overweight patients	1	Comment: the following statement: *"In case of overweight/obese patients the use of an intravenous anti-D product should be considered (see 161 section 4.4)"* is not needed here since it is the Core SPC of IV anti-D products. Proposed change (if any): Suppress sentence	Not accepted. The sentence is product - specific and it is intended for intravenous products that also have dosage recommendation for intramuscular use, as reported at the beginning of the subparagraph. To be more clear, the sentence has been modified as follow: *"In case of overweight/obese patients see section 4.4"*

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
176-180	1	Comment: Expand with following after "medicinal products containing IgA" Proposed change (if any): "……. medicinal products containing IgA. The exact magnitude of the risk of this type of reactions in patients with IgA deficiency is variable. There is no consensus among experts on the need for measurement of anti-IgA antibodies before administration of medicinal products containing IgA. The physician must therefore…….	Not accepted. The proposed sentence does not provide additional relevant information and for this reason is not consistent with the general approach followed for core SPCs.
187-199	1	Comment: see points above on line 19. Proposed change (if any): In our opinion, the warnings under point 4.4 regarding TEEs should be removed for the same reasons as described above. And *Patients with advanced age* are not pregnant.	Partly accepted. We don't agree with the proposal to remove the sentence. In any case the comment seems to be more related to anti-D immunoglobulins for intramuscular use than anti-D immunoglobulins for intravenous. However please see also the outcome of the *Overview of comments on draft core SPC anti D IM*. The following text is deleted (also for IMIg core SPC): *Patients with advanced age*