15 September 2016
EMA/CHMP/BPWP/379212/2016
Committee for Medicinal Product for Human Use

Overview of comments received on 'Draft guideline on the core SmPC for human Anti-D immunoglobulin for intramuscular use' (EMA/CHMP/BPWP/29205/2005 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	Sanquin Plasma Products
2	International Plasma Fractionation Association (IPFA), reference IP-16-104

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1. General comments

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

2. Specific comments on text

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
Lines 18-21	1; 2	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: [1. *Sanquin* / 2. *IPFA member Organizations]* since the 1960s and has been registered in the Netherlands as RheDQuin [1. *Sanquin]* since May 1997, thousands of patients have been treated with our product 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]	Not accepted. No contradictions are present since it is clearly stated that "*To date human anti-D immunoglobulin for intramuscular use has not been associated with risks of TEE (thromboembolic events)…".* However, since it is not possible to exclude thrombotic events especially in patients with risk factors, it is suggested to investigate "potential" procoagulant activity. If information on the level of procoagulant substances in the product is not available, their presence represents *per se* a potential additional risk factor for TEE in patients with pre-existing high risk factors. This text is intended to suggest the implementation of a proactive safety measure and not to introduce mandatory requirements for Companies.

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		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 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 feto-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	

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		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-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): remove warnings on TEE-risk	
Lines 43-48	1; 2	Comment: In this statement regarding the risk of TEEs, a contradiction is present since TEEs have not been observed for human anti-D immunoglobulin for intramuscular use. Proposed change (if any):	Not accepted. As explained for the previous comment, no contradictions are present since it is clearly stated that "*To date human anti-D*

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		In our opinion, only the first sentence is applicable and we suggest to remove the other sentences (lines 45-48).	*immunoglobulin for intramuscular use has not been associated with risks of TEE (thromboembolic events)...".* However, since it is not possible to exclude thrombotic events especially in patients with risk factors, it is suggested to investigate "potential" procoagulant activity. If information on the level of procoagulant substances in the product is not available, their presence represents *per se* a potential additional risk factor for TEE in patients with pre-existing high risk factors. This text is intended to suggest the implementation of a proactive safety measure and not to introduce mandatory requirements for Companies.
75 -79	2	Comment: Reason/rationale for requirement of IgG subclass distribution in anti-D immunoglobulin product is unclear. IgG1 and IgG3 anti-RhD subclasses have been shown to play a central role to clear effectively rhesus D positive red blood cells and to account for anti-D activity[1]. IgG1 being thought to be the main contributor for anti-D activity. IgG1 and IgG3 and are represented in physiological proportions in human anti-D immunoglobulin. Proposed change (if any): Mark as optional/remove.	Not accepted. We agree on the role of IgG1 and IgG3. Since IgG1 and IgG3 are represented in physiological proportions in human anti-D immunoglobulin, the IgG subclass distribution is an important information such as in SPC for human normal immunoglobulin.

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
		Literature: 1. The role of antenatal immunoprophylaxis in the prevention of maternal-foetal anti-Rh(D) alloimmunisation Giancarlo Maria Liumbruno, Angelo D'Alessandro, Federica Rea Vanessa Piccinini, Liviana Catalano, Gabriele Calizzani, Simonetta Pupella, Giuliano Grazzini Blood Transfus 2010; 8:8-16 DOI 10.2450/2009.0108-09	
119	2	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.
116-125	1; 2	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	Not accepted. Core SPC is intended to provide information to be included in the SPC of products authorized in several Countries with potential different

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		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 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.	national recommendations. For this reason the statement actually present in the core SPC is considered more appropriate.

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		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, 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.	
181	2	Comment: the words "*been used successfully to treat selected IgA deficient individuals*" imply it is used to manage IgA deficiency itself. Proposed change (if any): <u>"been used successfully in selected IgA deficient individuals"</u>	Accepted.

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180-185	1; 2	Comment: Recently Sandler et al. (2015) concluded in their article that the entity of IgA-related anaphylactic transfusion reaction has not been established by evidence-based medicine and therefore we propose to delete the paragraph with regard to IgA deficiency.[1] Moreover, no cases regarding the use of human anti-D immunoglobulin use and anaphylactic reactions in deficient IgA individuals have been reported worldwide. Proposed change (if any): Consider removing the paragraph on IgA-related anaphylactic transfusion reaction. Literature 1. Sandler SG1, Eder AF, Goldman M, Winters JL. The entity of immunoglobulin A-related anaphylactic transfusion reactions is not evidence based. Transfusion. 2015 Jan;55(1):199-204.	Not accepted. There are in literature several reports of anaphylactic reactions due to development of IgE against IgA in IgA deficient patients (Rutkowski K et al Allergy 2014; 69:; 1560-63; Ring J et al Clin Allergy 1988; 18:510-12; Sulakvelidze I et al. Allergy 1995; 50:981-83). For this reason we don't agree to delete this advice, already present in previous version of Core SPC.
193-205	1	Comment: see [two] points above. 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.	Not accepted. As explained above, the proposal to remove the warnings under point 4.4 regarding TEEs it is not accepted since it is clearly stated: "*Although thromboembolic events have not been observed for {(invented) name of product}…*". A general advice on how to manage patients with high risk of thrombotic events is given.
193-205	2	Comment: see [two] points above.	Partly accepted.

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		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.	The proposal to remove the warnings under point 4.4 regarding TEEs it is not accepted since it is clearly stated: "*Although thromboembolic events have not been observed for {(invented) name of product}…*". A general advice on how to manage patients with high risk of thrombotic events is given. The text "*Patients with advanced age*" is removed.
213-215	1; 2	Comment: This statement might need some more specification. For example, is the body mass index (BMI) used to determine the degree of obesity. In our opinion the lack of efficacy will not occur in patients with pre-obesity (BMI of 25-30). Proposed change (if any): We propose to change overweight/obese patients, in obese patients with a BMI of >30.	Not accepted. The degree of obesity is established on the basis of BMI (Body Mass Index: person's weight in kilograms divided by the square of height in meters). According to scientifically recognized CDC (Center for Disease Control and Prevention) definition, overweight range is defined as a BMI 25-29 and obese range as BMI ≥30 (http://www.cdc.gov/obesity/adult/defining.html). The text is in compliance with the coreSPCs of other immunoglobulin. No more details are considered needed.

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