21 March 2013
EMA/CHMP/BPWP/734487/2012
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Reflection paper on Immune Tolerance Induction in haemophilia A patients with inhibitors' (EMA/CHMP/BPWP/153137/2011)

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	International Plasma Fractionation Association (IPFA)
3	Biogen Idec Ltd
4	Swedish Orphan Biovitrum

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
2	IPFA appreciates the preparation of separate guidelines on “Immune Tolerance Induction in haemophilia A patients with inhibitors” and on the “Clinical investigation of factor VIII products”, addressing two different therapeutic approaches (replacement therapy for the blood coagulation disorder and drug therapy for the immunological disorder) even if both are treated by the same drug. With a separate guideline, more details can be provided, which is welcome for the study feasibility.	
2	We support the recognition of the assumption that inhibitor eradication is a therapeutic approach that has to be tailored for the individual patient; as well as that clear cut guidance on clinical trials to be performed to endorse an indication claim for immune tolerance induction cannot be given at present due to the complexity of unresolved scientific questions, the challenging nature of the management of inhibitor patients, the rarity of the condition, and the difficulty to undertake controlled trials. And therefore to reflect in the SmPC the immune tolerance induction experience with the specific product. We also appreciate the Case by case approach for the long-acting modified products	
2	Definition of immune tolerance induction success should indeed only be based on kinetics parameters returning to baseline, which is: inhibitors are no longer detectable and the recovery and half-life of FVIII are restored.	

Stakeholder no.	General comment (if any)	Outcome (if applicable)
2	The place for long-term prophylaxis following most of the high dose ITIs could be discussed, considering the difference between “success” and “eradication”.	
4	We agree with the proposition that regulatory decision on how of immune tolerance induction is reflected in the product information for clotting factor products should only be done on a case by case basis. It is also reasonable to state that no clinical trial experience with longer acting products exists at this stage. However, it is also true to state that the database for each individual product currently available and used in ITI varies and the data have not routinely been collected in a systemic and prospective way. Therefore, we suggest that all products, future and current, need to be evaluated on a case by case basis until the evidence base develops or changes.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
34	2	Comment: Real successes have been shown only with ITI and not with chemotherapeutics, corticosteroids and monoclonal antibodies only. Proposed change: Add after “Eradication of the inhibitor might be subject to immune tolerance induction (ITI) or immune-suppression.” the following: “Currently, the only way to eradicate inhibitors is ITI.”	Partly accepted. Eradication of the inhibitor might be subject to immune tolerance induction (ITI). ITI involves repetitive administration of factor VIII, in some therapeutic regimens in combination with immune-suppressive agents such as chemotherapeutics, corticosteroids or monoclonal antibodies.
54	2	Comment: Some literature data regarding the last identified risk factor that may affect the success rate of ITI, that is ‘type of FVIII product’ could be added. Proposed change: Add: “The German experience supported higher efficacy with FVIII/VWF concentrate (Ettingshausen and Kreuz, 2005) with a relatively good success in patients with poor-risk prognosis (Gringeri 2007, Kurth 2008, Greninger 2008). On-going randomised trials (the RESIST studies, Gringeri, Haemophilia 2007) are specifically addressing the impact of the presence of VWF in the FVIII concentrates used for ITI. Moreover, Some prospective ITI Registries (the Italian ITI	Not accepted. Point already made. Details of literature not needed.

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		Registry, Coppola J Thromb Haemost 2009) and the multinational Observational ITI - ObsITI - Study, started in Germany, Kreuz Thromb Res 2008) are investigating the predictors of ITI outcome, including the type of FVIII product.	
55	2	Comments: The sentence “A similar situation is reflected within Registry data: a high …” is not precise. Proposed change: Please provide the identity of the ‘Registry’ described	Partly accepted. This was not referring to a specific Registry. A similar situation is reflected within registry data: a high …”
73	2	Comments: While describing basic scientific aspects that remain open, please add other. Proposed change: Add new dots as other examples of unsolved general questions: • What is the minimum waiting period before to conclude that a treatment failed? • Are bypassing agents contributor of success? • What is the success definition for a second line of treatment (i.e. the use of a product which is different than the original factor VIII product)? • Role of adjuvant therapy to ITI: immunosuppressive or immunomodulatory procedures?	Partly Accepted. The text is giving examples of general questions and not an exhaustive list. Therefore, only the first 2 bullet points have been taken into the reflection paper.
77-78 and 96	2	Comments: A number of products indeed indicate some experience	Not accepted. Reference to the different sections of the SmPC is regarded as

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		of ITI in their SmPC. However, very few have a regulatory approved indication. Proposed change: These products may already have a wording regarding "treatment of inhibitor patients" included in the SmPC, and in France, for example, one has been approved for this indication since 2006."	adequate. Mentioning a single nationally authorized product is not appropriate.
103	2	Comment: "The success rate" is suggested to be not mentioned in the SPC, unless the information is robust. Proposed change: Success rate (mean + confidence interval) should be indicated, as well as the definition of success chosen.	Not accepted. If an applicant provides robust data for success rates, the parameters to be given in SmPC section 5.1 will be agreed by CHMP on a case by case basis.
103 - 106	1	Comment: The paper is stating that "*success rates*" should not be reported unless the available supportive data is consistent. We would propose that it should be possible to state, besides the total number of patients, also the actual number of patients that responded to treatment.	Not accepted. Number of patients that responded to treatment is another way of expressing "success rates", which is not considered to be meaningful with regard to the variety of influencing factors and the difficulties to compare these numbers between studies/products.
119 - 122	1	Comment: PPTA agrees to reflect management of inhibitor patients in paragraph 5.1 of the cSmPC supported by data	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
122-124	3	Comment: Regulatory decision on reflection of immune tolerance induction in the product information for products should only be done on a case by case basis. The database for each individual product used in ITI varies and the data are rather anecdotal and not investigated systemically in a prospective manor. Therefore it is not the case that only the long-acting products need to be evaluated on a case by case basis. It could be reasonable to state that currently no clinical trial experience with longer acting products exists. The later also applies to current products used in clinical practice, meaning even though clinical experience exists, a regulatory decision on reflection of immune tolerance induction in the product information for current products can also only be done on a case by case basis. Proposed change: “However, there is no ITI experience with the long-acting modified products, and therefore, regulatory decision on reflection of immune tolerance induction in the product information for those products can only be done on a case by case basis.” Should be changed to:	Partly accepted. However, there is no ITI experience with the long-acting modified products. Regulatory decision on reflection of immune tolerance induction in the product information is done on a case by case basis.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		"However, there is limited ITI experience with products, and therefore, regulatory decision on reflection of immune tolerance induction in the product information for all products can only be done on a case by case basis."	
122-124	4	Comment: See General Comment above Proposed change: However, there is limited ITI experience with clotting factor products, and therefore, regulatory decision on reflection of immune tolerance induction in the product information for all clotting factor products can only be done on a case by case basis."	Partly accepted. However, there is no ITI experience with the long-acting modified products. Regulatory decision on reflection of immune tolerance induction in the product information is done on a case by case basis.