EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

18 December 2014
EMA/CHMP/BPWP/697285/2014
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Guideline on core SmPC for human plasma derived and recombinant coagulation factor IX products' (EMA/CHMP/BPWP/1625/1999 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	Biogen Idec Ltd
2	International Plasma Fractionation Association (IPFA)
3	Novo Nordisk A/S
4	Pfizer Inc.
5	Swedish Orphan Biovitrum AB

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom

Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments – overview

Stakeholder no.	General comment	Outcome (if applicable)
1	The company welcomes the revisions to the guidelines based on the increased understanding of the variability in the use of assays to monitor factor IX levels. In particular this has arisen because of data from long-acting products currently in development and therefore the company believes it is an appropriate time to introduce a greater level of flexibility to the Core SPC to ensure that it is appropriate for short-acting and long-acting products. Where it would be appropriate to have non-mandatory wording which can be changed depending on the product, this has been indicated using the convention <…> as per the SmPC guidelines. Additionally, the company would consider useful to have information for transitioning from a previous product (e.g. short-acting to long-acting) given the number of products available and potential different half-lives.	Partly accepted. Under 2. Scope of the guideline, it is clarified that adaptations of the core SmPC guidance are needed in the case of long-acting products. It is too early to develop general statements about transitioning from a previous product.
2	IPFA welcomes the minor updates made to the Guideline on core SmPC for human plasma derived and recombinant coagulation factor IX products.	

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
108-120	1	Comments: Proposed change: To allow clear identification of the information related to the treatment monitoring (addition of heading and moving of paragraph before information on posology): Treatment monitoring During the course […] when changing the laboratory and/or reagents used in the assay. Posology Dose and duration […] and on patient's clinical condition. ~~During the course […] when changing the laboratory and/or reagents used in the assay.~~ The number of units of factor IX […].	Accepted.
108-113	3	Comment: In this posology section it is advised to guide dose and frequency of the product by factor IX activity determination. This would not be applicable for long-acting products with fixed dosing regimens. Proposed change: We suggest making this paragraph optional.	Not accepted. Experience from licensing of such products is needed before considering such a revision. See also general comments above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
110-111	4	Comment: The sentence “Dose based on bodyweight may require adjustment in underweight or overweight patients” should not be added to the core SmPC because it does not provide clear guidance as to how clinicians should change dosing based upon a patient’s departure from normal weight. Further, it may dilute the important direction measure of individual factor IX activity and adjusting dosing accordingly. There are now two directives: a) adjust weight-based dosing based on FIX activity and b) adjust weight-based dosing based on departure from normal body weight. The second directive ‘b’ adds no additional information and may detract from simply following ‘a’. Proposed change: We propose to delete the statement.	Not accepted. It is considered helpful to include this general statement.
109, 145 table (3), 221 and 225	3	Comment: Apart from continuous infusion sometimes used for non-modified products in the surgery setting, administration of factor concentrates are generally done by injections lasting a few minutes depending on volume. Proposed change: We suggest replacing “infusion” with “injection”.	Not accepted. This is a rapid revision for a specific purpose and not a general reopening of the core SmPC text.
111-113	1	Comments: The word “precise” should be replaced by “accurate” since this better describes the monitoring required in situations of major surgical interventions.	Not accepted. This is a rapid revision for a specific purpose and not a general reopening of the core SmPC text.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: In the case of major surgical interventions in particular, ~~precise~~ accurate monitoring of the substitution therapy by means of coagulation analysis (plasma factor IX activity) is indispensable.	
120	3	Comment: Due to product-specific differences in the described assay variability further guidance could be supplied. Proposed change: We propose to add: “For product specific recommendation/information on assays please refer to Marketing Authorisation holders homepage (incl. name of homepage).”	Not accepted. The guidance provided in the core SmPC indicates that the text can be supplemented with product-specific information. This is considered sufficient.
133-160	3	Comment: For long-acting products, dose levels and frequency are expected to differ significantly from non-modified factor concentrates. Proposed change: We suggest making this paragraph optional.	Partly accepted. Under 2. Scope of the guideline, it is clarified that adaptations of the core SmPC guidance are needed in the case of long-acting products.
Table	1	Proposed additions to allow product specific recommendations (e.g. long-acting products). Frequency of doses (hours)/Duration of therapy (days): - For early haemarthrosis, muscle bleeding or oral bleeding:	See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		[Product specific] <Repeat every 24 hours. At least 1 day,> until the bleeding episode as indicated by pain is resolved or healing is achieved. - For more extensive haemarthrosis, muscle bleeding or haematoma: *[Product specific]* <Repeat infusion every 24 hours for 3-4 days or more> until pain and acute disability are resolved. - For minor surgery including tooth extraction: *[Product specific]* <Every 24 hours, at least 1 day,> until healing is achieved. - For major surgery: *[Product specific]* <Repeat infusion every 8-24 hours until adequate wound healing, then therapy for at least another 7 days> to maintain a factor IX activity of 30% to 60% (IU/dl).	
146-160 (the table)	5	Comment: Where rFIX concentrates may have half-lives that differ from non-modified FIX concentrates, the frequency of dosing may differ from what is stated in the table. In these cases, the deviation from the general statement of frequency must be justified by product-specific information. We therefore propose that it should be considered to take products with different half-lives into account and allow for flexibility	See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		with regards to the dosing intervals.	
175-182	3	Comment: Continuous infusion does not apply to the long-acting products. Proposed change: We suggest making this paragraph optional.	Not accepted. Paragraph is already optional so no change is needed.
186-195	2	Comment: The draft core SPC foresees that - (line 192) *"<The safety and efficacy of {(invented) name} in children aged x to y <months, years> have not yet been established*." - (Line 402-404) "*[Product specific: The text should be in line with the Paediatric Regulation and the SmPC guideline. In* 403 *case of a full waiver or any deferral, include the standard statement in the SmPC guideline.]"* And this is welcome. However, contrary to the whole European regulation as inspired by the usual requirements of the PDCO (the EMA paediatric Committee), FVIII and FIX developments, as required by the Notes for guidance (Clinical investigation of recombinant and human plasma-derived factor VIII products *(replacing CPMP/BPWG/198/95 and CPMP/BPWG/1561/99) and*	No modification of core SmPC is requested.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Clinical investigation of recombinant and human plasma-derived factor IX products *(replacing CPMP/BPWG/198/95 and CPMP/BPWG/1561/99)*), are in practice the only occasion in where deferrals or waivers for paediatric studies have not been allowed. According PDCO policies, waivers for coagulation factor studies could be granted on the ground that "the specific medicinal product does not represent a significant therapeutic benefit as clinical studies(s) are not feasible in the specified paediatric subset(s)", based on the fact that experience of haemophilia products in children is highly known and could be extrapolated from data accumulated in adults. Proposed change: Consistency is asked between Notes for Guidance and Core SPC, by updating the Notes for Guidance by allowing deferral or waivers for paediatric development of coagulation products, including FIX, as or any medicinal product (not requesting mandatory pre-registration studies in paediatric populations.	
268-270	1	Biogen Idec considers that the currently available evidence is not sufficient to warrant an update to the core SmPC template for recombinant coagulation factor IX products. Biogen Idec conducted an evaluation of the available published literature regarding a possible association of increased	Not accepted. Statement is included due to the demographic change in haemophilia patients and cardiovascular events reported in PSURs.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		cardiovascular risk in haemophilic patients with cardiovascular risk factors and factor IX substitution (replacement) therapy. This association was primarily assessed in a published review of the literature by Girolami, et al. (2005). Their search of the literature yielded 13 haemophilia B patients with myocardial infarction (MI) and 1 patient with a cerebrovascular accident. In 5 of the 13 patients with an MI, the event occurred during or after the infusion of prothrombin complex (PC) concentrates. In 3 additional patients the event occurred after infusion of plasma, Feiba or cryoprecipitate supernatant. In 4 of the 13 patients, MI occurred without concentrate infusion and in 1 patient the concomitant medication was not reported. The cerebrovascular accident was reported after orthopaedic surgery. Based on their analysis of the literature, the authors concluded that myocardial infarction may occur in haemophilia B patients and that invasive coronary artery therapeutic procedures may be carried out without complications. In this published review, the occurrence of cardiovascular events following administration of plasma derived clotting factor products was observed. However, several limitations to these data are noted including small sample size and the lack of a strong comparator population or group. None of the patients in this series were reported to have received	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		recombinant factor IX products. Biogen Idec considers that the current evidence, including the literature review presented by Girolami, et al, is not sufficient to warrant template update for the SmPC for factor IX products regarding a possible increase in cardiovascular risk in patients with existing cardiovascular risk factors. Literature case reviews are considered to be one of the lowest levels of evidence for determining whether a drug is exerting a safety class effect (McAllister, 1999). In particular, there is no strong evidence to support an association between increased cardiovascular risk and infusion of recombinant FIX products. The current rFIXFc Biogen Idec Core Data Sheet addresses the potential for thromboembolic complications during rFIXFc therapy. Biogen Idec believes current labelling is adequate to inform prescribers and patients about the potential risk of thromboembolic complications in patients on rFIXFc therapy. Thromboembolism is already listed as a known risk in the Core SPC which is considered adequate to inform prescribers and patients about the potential risk of thromboembolic complications in patients on replacement FIX therapy.	

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		References: Girolami, A.; M. Randi.; E. Ruzzon; E, Zannon; B. Girolami. (2005) Myocardial Infarction, Other Arterial Thrombosis and Invasive Coronary Procedures, in Hemaophilia B: A Critical Evaluation of Reported Cases. Journal of Thrombosis and Thrombolysis: 20(1), 43–46. McAllister, F.; Laupacis, A.; Wells, G.; Sackett, D. (1999) Guidelines for determining whether a drug is exerting (more) than a class effect. JAMA: 282(14), 1371-1377.	
268-270	3	Comment: We find no literature to support that in patients with existing cardiovascular risk factors, substitution therapy with FIX may increase the cardiovascular risk even further. Proposed change: We suggest not including section “Cardiovascular events”, or alternatively, include in prior section supporting increased surveillance line 264:” …in patients with *increased cardiovascular risk*, liver disease…”.	Not accepted. See above.
268-270	4	Comment: High level of FIX concentration was associated to incremental venous thrombosis risk in non-haemophilic subjects (van Hylckama Vlieg A et al, Blood 2000; 95:3678-3682). In addition in a mouse model, myocardial fibrosis was associated with overexpression of FIX (Ameri A et al, Blood 2003; 101:1871-1873). These examples do not apply for Haemophilia B patients, where the FIX treatment replaces the missing FIX.	Not accepted. See above.

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
		Proposed change: We propose to delete the statement.	
268-270	5	Comment: This risk may differ between concentrates depending on their content of activated FIX. Thus, a class warning may not be warranted.	Not accepted. See above.
319	1	Proposed addition of non-mandatory text to allow specific product information: *[Product specific]* <{(Invented) name} has no influence on the ability to drive and use machines.>	Not accepted. Core SmPCs are guidance documents and appropriately justified departures from the guidance can be accepted.
401	1	Proposed addition to allow specific product information (e.g. mechanism of action for long-acting products): *[Product specific information should be added]*	Partly accepted. Under 2. Scope of the guideline, it is clarified that adaptations of the core SmPC guidance are needed in the case of long-acting products.