27 June 2024

Submission of comments on 'Guideline on core SmPC for human plasma derived and recombinant coagulation factor IX products' (EMA/CHMP/BPWP/1625/1999 rev. 3)

Comments from:

Name of organisation or individual
- European Haemophilia Consortium - Plasma Protein Therapeutics Association (PPTA) on behalf of member companies BioProducts Laboratory, BPL, CSL Behring, Grifols, Kedrion, Takeda - Pfizer

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1. General comments

Stakeholder number	General comment (if any)	Outcome (if applicable)
PPTA	The core SPC removes reference to PUPs, however the new text under "Treatment Monitoring" seems to be mainly directed towards the next generation recombinant factor IX products. There is also a new sentence about the product-specificity of annualised bleeding rates (=ABR; in the section on Pharmacodynamic Properties). Given that some regulators have previously valued lower ABR as a measure of benefit, it is unclear how it could be used within an ethical treatment regime, if the new product ABR cannot be compared with the previous ABR while being treated with a different product.	- Of note, the subsection on treatment monitoring does not refer to a specific group of FIX products and was already included in the previous revision of the guideline. - In the core SmPC guideline the following statement has been introduced (Section 5.1): "Of note, ABR (annualized bleeding rate) is not comparable between different factor concentrates and between different clinical studies". This statement is not a valuation of this endpoint but indicates that bleeding rates are not necessarily comparable between different authorised products and clinical trials. The reason behind this statement is that this parameter currently lacks standardisation and that comparison e.g. across clinical trials (different study populations, different regions etc.) may not be scientifically sound.
Pfizer	Prophylaxis regimen in section 4.2 Posology and method of administration: 'For long term prophylaxis against bleeding in patients with **severe** haemophilia B, the usual doses are 20 to 40 IU of factor IX per kilogram of body weight at intervals of 3 to 4 days.' – Core SmPC 'For long term prophylaxis against bleeding in patients with severe haemophilia B, the usual doses are {x} to {y} IU of factor IX per kg of body weight at intervals of {x} to {y} days.' – Core SmPC The guideline on the clinical investigation of recombinant and human plasma-derived factor IX products require applicants to evaluate clinical efficacy	The FIX GL recommends including Haemophilia B patients in clinical trials with factor IX ≤2%. This recommendation has been made only for clinical trial feasibility reasons and does not affect definitions of haemophilia severity nor does affect per se general treatment recommendations.

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	in patients 'suffering from **haemophilia B (factor IX ≤ 2%)**' (in review, version EMA/CHMP/BPWP/144552/2009 Rev. 1, Corr. 1) Considering that severe patients are classified as patients with <1% factor activity level (according to ISTH and EHC guidelines), there seems to be a disconnect between the study population and the language being used in the core SmPC guidelines.	

2. Specific comments on text

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
4-5	European Haemophilia Consortium	Comment: The title should include long-acting to clarify it also covers this category of products. Proposed change: Guideline on core SmPC for human plasma derived, recombinant and long-acting coagulation factor IX products.	Not agreed. The core SmPC guideline covers recombinant and human plasma-derived factor IX products in general, irrespective of their individual PK properties.
82-83	European Haemophilia Consortium	Comment: The details of the one-stage clotting test should be included. Specifically, details of the reagents and reagent manufacturer used in the clotting tests should be included.	Not agreed. This information is not considered essential on the SmPC level for proper administration of the medicinal product. Of note, it is already clarified in Section 4.2 that "*factor IX activity results can be significantly affected by both the type of aPTT reagent and the reference standard used in the assay*".
126-128	European Haemophilia Consortium	Comment: Editorial: The *text* should be in italics as it is guidance on when to use the following text in the SmPC	Agreed. The statement regarding one-stage clotting assay (reagents) is usually included in case of recombinant products (partly with specific additions) whereas it is usually not included in case of plasma-derived products. The change is also in accordance with EMA Guideline on

Line number(s) of the relevant text	Stakeholder number	Comment and rationale; proposed changes	Outcome
			core SmPC for human plasma derived and recombinant coagulation factor VIII products in its latest revision.
129 and 132	European Haemophilia Consortium	Comment: Editorial: Text should start with < and finish with > as it is not required for all products.	Agreed (see above).
265-267	European Haemophilia Consortium	Comment: Text should be deleted as the traceability sentence that followed has been replaced by a sub-heading on traceability at the start of 4.4.	Agreed.