EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

23 July 2015
EMA/CHMP/BPWP/336355/2014
Committee for Medicinal Products for Human Use (CHMP)

# Overview of comments received on 'Guideline on core SmPC for human fibrinogen products' (EMEA/CHMP/BPWP/691754/2013 Rev 1)

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

| Stakeholder no. | Name of organisation or individual |
|---|---|
| 1 | CSL Behring GmbH |
| 2 | Prof. Flora Peyvandi |
| 3 | Prof. Vladimir Cerny, MD, PhD, FCCM<br>on behalf of Czech Society of Intensive Care Medicine<br>Prof. Karel Cvachovec, MD, PhD, MBA<br>on behalf of Czech Society of Anesthesiology and Intensive Care |
| 4 | Biotest AG |
| 5 | Sibylle Kozek-Langenecker, Cesar Aldecoa Alvarez Santullano, Edoardo de Robertis, Dietmar Fries, Thorsten Haas, Georgina Imberger, Matthias Jakob, Marcus Lancé, Juan Llau, Sue Mallet, Niels Rahe-Meyer, Phillippe Van der Linden, Patrick Wouters (authors of the first edition of *"Management of severe perioperative bleeding: guidelines from the European Society of Anaesthesiology"*, published in June 2013)<br><br>Donat R. Spahn, Bertil Bouillon, Vladimir Cerny, Timothy J. Coats, Jacques Duranteau, Enrique Fernández-Mondéjar, Beverley J. Hunt, Radko Komadina, Giuseppe Nardi, Edmund Neugebauer, Yves Ozier, Louis Riddez, Arthur Schultz, Jean-Louis Vincent, Rolf Rossaint (authors of the third update of "*Management of bleeding and coagulopathy following major trauma: an updated European Guideline*", published in April 2013) |

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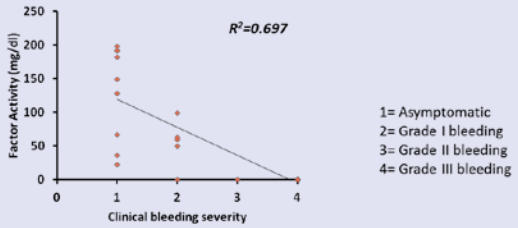
# 1. General comments – overview

| Stakeholder no. | General comment (if any) | Outcome (if applicable) |
|---|---|---|
| 2 | I would like to bring your attention to the results obtained by the EN-RBD project published on J Thromb Haemost 2012; 10: 615–21. This cross-sectional study on 46 patients with fibrinogen deficiency showed a very good correlation between the level of residual fibrinogen activity in plasma and the severity of bleeding episodes. You can read that level >1g/L were necessary to avoid bleeding episodes, with patients with >1g/L remained asymptomatic.<br><br>  <br><br><br>Linear regression analysis: ***adjusted*** for age, gender, and country where diagnosis was made<br><br>\| Factor deficiency \| Beta (95% CI) \| Factor activity for Asymptomatic patients (95% CI) \| Factor activity for Grade I bleeding (95% CI) \| Factor activity for Grade II bleeding (95% CI) \| Factor activity for Grade III bleeding (95% CI) \|<br>\| --- \| --- \| --- \| --- \| --- \| --- \|<br>\| Fibrinogen, mg/dl (n=26) \| -40.22 (-54.24 to -26.19) \| **113.40 (22.80 to 204.01)** \| 73.19 (0 to 164.14) \| 32.97 (0 to 126.39) \| **0 (0 to 90.61)** \|<br><br>This result was also confirmed by the FVIII&FIX SSC ISTH expert group that published an official SSC communication on RBDs classification in 2012 (J Thromb Haemost 2012; 10: 1938-43)<br>Therefore my recommendation would be to change the minimum level reported at page 3, line 95 from “0.5 – 1.0 g/l” to “1 g/l”.<br>Please do not hesitate to contact me for any further comments. | Not accepted.<br><br>The references quoted by Prof. Peyvandi do not contain the figure used in the argument put forward.<br><br>Also, the correlation claimed in the figure shown is not agreed.<br><br>However, the statement at line 94-95 of the draft core SmPC has been deleted (see below). |

## 2. Specific comments on text

| Line no. | Stakeholder no. | Comment and rationale; proposed changes | Outcome |
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| 70–77 | 3 and 5 | Treatment and prophylaxis of bleeding in patients with congenital hypo-, dys- or afibrinogenaemia with bleeding tendency.<br><br>As complementary therapy to management of uncontrolled severe haemorrhage in acquired hypofibrinogenaemia, for example:<br>a. Increased consumption of fibrinogen associated with otherwise uncontrolled life-threatening bleeding in obstetric complications<br>b. Impaired synthesis of fibrinogen in patients with severe hepatic insufficiency<br><br>Comment:<br>*In order to improve clarity, we suggest using subheadings to divide the indications into congenital and perioperative fibrinogen deficiency.*<br><br>*The phrase 'As complementary therapy' implies that fibrinogen concentrate is a secondary, as opposed to first-line, treatment. We therefore propose rephrasing that sentence.*<br><br>*We have suggested amended phrasing and additional examples of situations in which fibrinogen concentrate should be administered to control bleeding, in line with* | Not accepted.<br><br>Rationale: the proposal to introduce new indications of peri-operative bleeding and cardiopulmonary bypass would require substantive data<br>It is not agreed that introduction of sub-headings improves the content of the core SmPC |

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| | | *recent guidelines (Kozek-Langenecker et al., 2013, Eur J Anaesthesiol; Spahn et al., 2013, Crit Care).*<br><br>Proposed change (if any):<br>Congenital fibrinogen deficiency<br>Treatment and prophylaxis of bleeding in patients with congenital hypo-, dys- or afibrinogenaemia with bleeding tendency.<br><br>Fibrinogen deficiency in perioperative bleeding<br>For the management of bleeding ~~As complementary therapy to management of uncontrolled severe haemorrhage in acquired hypofibrinogenaemia~~as a result of perioperative fibrinogen deficiency, for example:<br>a. Haemorrhage following cardiopulmonary bypass<br>~~Increased consumption of fibrinogen associated with otherwise uncontrolled life-threatening bleeding in obstetric complications~~<br>~~b. Impaired synthesis of fibrinogen in patients with severe hepatic insufficiency~~ | |
| 81–82 | 3 and 5 | Treatment should be initiated under the supervision of a physician experienced in the treatment of coagulation disorders.<br><br>Comment:<br>*We have suggested an amendment to clarify that the physician supervising treatment should be experienced in prophylaxis as well as treatment, and amended* | Not accepted.<br><br>Rationale: it is preferred to not introduce restrictions on clinical practice, as described |

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| | | *'coagulation disorders' to 'bleeding' to cover bleeding management in the perioperative setting as well as congenital situations.*<br><br>Proposed change (if any):<br>Treatment and prophylaxis of afibrinogenaemia and hypofibrinogenaemia should be initiated under the supervision of a physician experienced in the treatment of congenital coagulation disorders. In perioperative settings, treatment should be initiated under the supervision of a physician experience in perioperative bleeding management. | |
| 86-87 | 2 | Comment: same data on PK studies (3 references) should be reported<br><br>Proposed change (if any): | Not accepted.<br><br>Section 5.2 of the SPC is for PK data (and already contains some information on this) |
| 94–95 | 3 and 5 | Normal plasma fibrinogen level is in the range of 1.5-4.5 g/l. The critical plasma fibrinogen level below which haemorrhages may occur is approximately 0.5 – 1.0 g/l.<br><br>Comment:<br>*While we feel that the information given in the statement "*The critical plasma fibrinogen level below which haemorrhages may occur is approximately 0.5 – 1.0 g/l.*" is accurate in congenital settings, we are concerned that this level is too low for perioperative fibrinogen deficiency. Recent guidelines for controlling* | Not accepted.<br><br>Fibrinogen may be measured by several different methods (Clauss method, antigen-antibody detection, point-of-care testing) each of which is associated with its own result and reference interval.<br><br>Furthermore, The request for fibrinogen to be given in acquired hypofibrinogenamia when <1.5 g/L is based on EU critical care reviews that graded the evidence as "1C" i.e. recommendation on low or very-low quality of evidence (recommendation may change as evidence becomes available). However, there is also |

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| | | *bleeding in perioperative and trauma settings recommend treating with fibrinogen concentrate when significant bleeding is accompanied by a plasma fibrinogen level of <1.5–2.0 g/l or when a functional fibrinogen deficiency is observed (Kozek-Langenecker et al., 2013, Eur J Anaesthesiol; Spahn et al., 2013, Crit Care).*<br><br>Proposed change:<br>Congenital fibrinogen deficiency<br>The critical plasma fibrinogen level below which haemorrhages may occur is approximately 0.5 – 1.0 g/l.<br><br>Fibrinogen deficiency in perioperative settings<br>Administration of fibrinogen concentrate should be considered when significant bleeding is accompanied by suspected low fibrinogen concentration (plasma fibrinogen level of <1.5–2.0 g/l) or thromboelastic signs of functional fibrinogen deficit. | no strong evidence to support <0.5-1.0g/L as stated in the core SmPC.<br><br>In conclusion, it is preferred to delete reference to the reference interval and 'target concentration'. Thus:<br>~~*Normal plasma fibrinogen level is 1.5 – 4.5 g/l. The critical plasma fibrinogen level below which haemorrhages may occur is approximately 0.5 – 1.0 g/l*~~ |
| 94-95 | 1 | Comment:<br><br>See supporting documentation and attached literature<br><br>Proposed change:<br><br>Normal plasma fibrinogen level is ~~in the range of~~between 1.5 – 4.5 g/l. In congenital deficiency, ~~T~~the critical plasma fibrinogen level below which spontaneous haemorrhages may occur is approximately | Not accepted.<br>See comments above. |

| Line no. | Stakeholder no. | Comment and rationale; proposed changes | Outcome |
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| | | 0.5 – 1.0 g/l. In acquired deficiency, fibrinogen concentrate should be given if significant bleeding is accompanied by a plasma fibrinogen level of less than 1.5 to 2.0 g/l. | |
| Section 4.2 Posology | 1 | Comment:<br><br>See supporting documentation<br><br>Proposed change:<br><br>Normal plasma fibrinogen level is between ~~in the range of~~ 1.5 ~~–~~and 4.5 g/l. In congenital deficiency, a plasma level of > 1 g/l appears sufficient to prevent spontaneous bleeding episodes. In acquired deficiency, fibrinogen concentrate should be given if significant bleeding is accompanied by a plasma fibrinogen level of less than 1.5 to 2.0 g/l.The critical plasma fibrinogen level below which haemorrhages may occur is approximately 0.5 – 1.0 g/l. | a. The Company concurs with the reference interval for fibrinogen 1.5 - 4.5 g/L. Issue resolved.<br><br>b. For congenital deficiency, the Company recommends the wording ">1 g/L appears sufficient" implying that the evidence is not fully established on this point.<br>It is also recognised that bleeding in the context of congenital deficiency shows much variability from patient to patient with regards to fibrinogen concentration.<br>For these reasons, it is preferred not to adopt the wording of the Company. This issue may be kept under review.<br><br>c. For acquired deficiency, the Company recommends "fibrinogen concentrate should be given if significant bleeding is accompanied by a plasma fibrinogen less than 1.5 - 2.0 g/L"<br>The proposal of the Company is based on:<br>Rossaint et al. Management of bleeding following major trauma: an updated European guideline Critical Care 2010;14:R52<br>The recommendation of Rossaint et al is grade 1C i.e. strong recommendation (may change when higher quality evidence becomes available), low-quality or very low-quality evidence.<br>This grade of recommendation is not considered adequate to change the current core SmPC. |

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| | | | Moreover, there is concern that management of trauma-induced severe bleed with fibrinogen is not associated with improved survival.<br>Reference: Wafaisade A et al. Administration of fibrinogen concentrate in exsanguinating trauma patients is associated with improved survival at 6 hours but not at discharge. J Trauma Acute Care Surg. 2013;74(2):387-3. This issue may be kept under review.<br><br>Overall, it is preferred to maintain the wording of section 4.2 (apart from the one deletion of line 94-95 of the draft core SmPC) until more robust evidence is obtained. |
| 95 | 2 | Proposed change: The critical plasma fibrinogen level below which haemorrhages may occur is approximately 1 g/l | Not accepted. See comments above. |
| 107 | 1 | Comment:<br><br>Brackets missing in formula.<br><br>Proposed change:<br><br>Dose (g) = [(desired levels (g/l) – baseline level (g/l)] x 1/recovery (g/l / g/kg) x body weight (kg). | Accepted.<br><br>Rationale: inclusion of square brackets, as shown, is technically correct |
| 107 | 4 | Comment: In the formula for dose calculation the missing bracket should be included.<br><br>Proposed change (if any):<br>Dose (g) = [desired levels (g/l) – baseline level (g/l)] x 1/recovery (g/l / g/kg) x body weight (kg) | Accepted.<br><br>See above. |

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|---|---|---|---|
| 113–116 | 3 and 5 | The biological half-life of fibrinogen is 3-4 days. Thus, in the absence of consumption, repeated treatment with human fibrinogen is not usually required. Given the accumulation that occurs in case of repeated administration for a prophylactic use, the dose and the frequency should be determined according to the therapeutic goals of the physician for a given patient.<br><br>Comment:<br>*The statement '*in the absence of consumption*' is misleading, as in the absence of fibrinogen consumption there would be no need to administer fibrinogen concentrate.*<br><br>*In order to improve clarity, we suggest using subheadings to divide the information into congenital and perioperative fibrinogen deficiency.*<br><br>Proposed change:<br>Prophylactic~~is~~ administration in congenital fibrinogen deficiency<br>The biological half-life of fibrinogen is 3-4 days. ~~Thus, in the absence of consumption, repeated treatment with human fibrinogen is not usually required. Given the accumulation that occurs in case of repeated administration for a prophylactic use, t~~The dose and the frequency of administration for prophylaxis should be determined according to the therapeutic goals of the physician for a given patient. | Not accepted.<br><br>Rationale: the core SmPC statement that "*dose and the frequency should be determined according to the therapeutic goals of the physician for a given patient*" is already present. |

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| | | Fibrinogen deficiency in perioperative settings<br>The dose and the frequency of administration should be determined according to the therapeutic goals of the physician for a given patient. | |
| 118 | 3 and 5 | 2. Treatment of bleeding<br><br>Comment:<br>*Amendment proposed to clarify this section applies to both congenital and perioperative fibrinogen deficiency settings.*<br><br>Proposed change:<br>2. Treatment of bleeding in patients with congenital hypo-, dys- or afibrinogenaemia, and in patients with fibrinogen deficiency in perioperative settings | Not accepted.<br><br>Rationale: the proposed changes are consequent to proposed changes in section 4.1 that were not accepted. |
| 147–149 | 3 and 5 | There is a risk of thrombosis when patients, with either congenital or acquired deficiency, are treated with human fibrinogen particularly with high dose or repeated dosing. Patients given human fibrinogen should be observed closely for signs or symptoms of thrombosis.<br><br>Comment:<br>*We have suggested amending the text in order to remain consistent with the proposed changes to section 4.1*<br><br>Proposed change: | Not accepted.<br><br>The proposed wording for section 4.1 from this respondent was not accepted. Section 4.4 is linked to 4.1. |

| Line no. | Stakeholder no. | Comment and rationale; proposed changes | Outcome |
|---|---|---|---|
| | | There is a risk of thrombosis when patients, with either congenital fibrinogen deficiency or fibrinogen deficiency in a perioperative setting ~~or acquired deficiency~~, are treated with human fibrinogen particularly with high dose or repeated dosing. Patients given human fibrinogen should be observed closely for signs or symptoms of thrombosis. | |
| 147-149 | 2 | Comment: The risk of thrombosis is particularly high in patients with dysfibrinogenemia, therefore activity and antigen levels of patients' plasma should be determined for a correct diagnosis | Not accepted.<br><br>It is preferred to not give detailed advice on clinical management: this ought to be within the knowledge of the specialist physician. |
| 157–160 | 3 and 5 | Acquired hypofibrinogenaemia is associated with low plasma concentrations of all coagulation factors (not only fibrinogen) and inhibitors and so treatment with blood products containing coagulation factors should be considered (with or without administration of fibrinogen concentrate). Careful monitoring of the coagulation system is necessary.<br><br>Comment:<br>*We have suggested amending the phrase "Acquired hypofibrinogenaemia" in order to remain consistent with the proposed changes to section 4.1*<br><br>*At present the phrasing (particularly the section in brackets) suggests that fibrinogen concentrate is not* | Not accepted.<br><br>Rationale: the proposed changes are consequent to proposed changes in section 4.1 that were not accepted. |

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|---|---|---|---|
| | | *the first-line treatment as non-specific replacement with general blood products is proposed as an alternative treatment. We have proposed amendments to this section to clarify this issue.*<br><br>Proposed change:<br>~~Acquired hypofibrinogenaemia~~Fibrinogen deficiency in perioperative settings ~~is~~ may be associated with low plasma concentrations of all coagulation factors (not only fibrinogen) and inhibitors and so treatment with blood products containing coagulation factors ~~should~~ could be considered ~~(with or without administration of fibrinogen concentrate)~~. Careful monitoring of the coagulation system is necessary. | |
| 157-160 | 1 | Comment:<br><br>See supporting documentation and attached literature<br><br>Proposed change:<br><br>Acquired hypofibrinogenaemia is associated with low plasma concentrations of all coagulation factors (not only fibrinogen) and inhibitors and so treatment with blood products containing coagulation factors should be considered ~~(with or without administration of fibrinogen concentrate)~~. Careful monitoring of the coagulation system is necessary. | Accepted.<br><br>Rationale: deletion of the highlighted words does not change meaning. |