10 November 2016
EMA/452872/2016
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Guideline on clinical investigation of medicinal products for prevention of venous thromboembolism (VTE) in non-surgical patients (formerly CPMP/EWP/6235/04 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	LEO Pharma A/S
2	Medicines Evaluation Board of the Netherlands

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1. General comments - overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	LEO Pharma A/S (hereafter referred to as LEO) welcomes the opportunity to give input to this draft guidance document. We respectfully submit the detailed comments below, for your consideration.	

2. Specific comments on text

Line number(s) of the relevant text	Comment number Stakeholder number	Comment and rationale; proposed changes	Outcome
70	Comment 1 Stakeholder 1	Comment: "…long-term sequels" Proposed change (if any): "…long-term sequelae"	Accepted.
74	Comment 2 Stakeholder 1	Comment: 'Distal DVTs are considered less serious unless propagating proximally.' Please consider rephrasing, as proposed below, in line with Simmoneau et al. (N Engl J Med. 1997 Sep 4;337(10):663-9, table 1) Proposed change (if any): 'Distal DVTs, whilst less serious than proximal, can also cause large and sometimes fatal PE'	Partly accepted. It is acknowledged that (infrequently), distal DVTs can also cause PE, but this happens to a much lower frequency than in case of proximal DVT. The sentence has been rephrased as "Distal DVTs are **usually** less serious, unless propagating proximally"
98	Comment 3 Stakeholder 1	Comment: "post-phlebitic syndrome" Proposed change (if any): Should it be "post-thrombotic syndrome"?	Accepted.
122-142	Comment 4 Stakeholder 2	Comment: pregnancy and postpartum period are considered predisposing risk factors for VTE. Proposed change (if any): pregnancy and postpartum period should be added as presdiposing risk factors for VTE.	Not accepted. The Padua score (ref. 12 of the guideline) does not include pregnancy as an important predisposing factor for VTE. It is true that during pregnancy there may be a transient physiological hypercoagulability during the first trimester to protect women against the bleeding challenges associated with miscarriage and childbirth. However,

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			indication for anticoagulation during pregnancy only includes a current thrombosis (treatment), a history of thrombosis, thrombophilia, and a history of poor pregnancy outcome (secondary prevention), or risk factors for postpartum thrombosis (general factors for VTE). The list that appears in the guideline already includes previous VTE or associated thrombophilia. Therefore, the inclusion of pregnancy itself (without the presence of concomitant risk factors like previous VTE or thrombophilia) in the list of important predisposing factors for VTE is not agreed.
124	Comment 5 Stakeholder 1	Comment: It should be considered that these risk factors are also relevant for non-hospitalized patients. In general, the guidance is not clear on hospitalized patients vs. non hospitalized patients	Accepted. The list of risk factors are referring to "hospitalised medical patients" (ref. 12 of the document). Some of these risk factors are specific of hospitalised patients, because they are referring to the causes that trigger hospitalisation (e.g.: acute myocardial infarction or stroke, etc.), therefore, not all of these risk factors are applicable to outpatients. We have added *"... as well as in clinical trials in outpatients (applicable for general VTE risk factors)*".

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130	Comment 6 Stakeholder 1	Comment: It would be preferred if cancer is divided into advanced cancer (locally advanced/metastatic) and other forms of active cancer Proposed change (if any):	Not accepted. The guideline includes the term "active cancer" as included in the reference that supports the list of risk factors. The stakeholder's proposal has not been supported with appropriate references.
133	Comment 7 Stakeholder 1	Comment: thrombophyilic Proposed change (if any): thrombophyllic	Accepted.
145 - 152	Comment 8 Stakeholder 1	Comment: There is no mention of Pregnancy. Pregnancy is often a non- surgical reason for prophylaxis against VTE; please consider to include. Furthermore, there is no mentioning of **renal** impairment being risk factor nor as a factor in patient selection. (although the renal function subgroup is mentioned - line 420 - for analysis.) Please consider to include.	Not accepted. For pregnancy, please see answer to previous comment for lines 122-142. With respect to renal impairment, the more relevant clinical practice guideline for VTE prophylaxis in medical patients (Kahn et al. 2012; Ref. 1 of the draft guideline) as well as the PADUA score (Barbar et al, 2010; Ref. 12 of the draft guideline) do not include renal impairment as relevant risk factor for thrombosis in medical patients. The mention to renal function subgroups in line 420 is related to potential differences in drug exposure and bleeding risk (e.g.: already documented for LMWH or fondaparinux).
164	Comment 9 Stakeholder 1	Comment: Suggest to include pregnancy and renal impairment as well	Not accepted. Please, see previous answer.

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212	Comment 10 Stakeholder 1	Comment: It reads as if asymptomatic distal DVT would be included as an efficacy outcome, should be rephrased	The wording is correct. Asymptomatic distal DVT can be included as an efficacy outcome, although only recommended in exploratory trials (section 5.2 of the guideline).
236	Comment 11 Stakeholder 1	Comment: Proposed change (if any): In case of 'suspected fatal PE,' effort should be made to obtain an autopsy ***report*** to confirm the diagnosis. Unless PE has been excluded, it will be difficult to attribute any death to non-PE causes.	Accepted.
258 – 261	Comment 12 Stakeholder 1	Comment: 'VTE-related death (non-inferiority trials) or all-cause death (superiority trials)'. The text is suggested to be revised. It is not directly understood why all cause of deaths is included and why to differentiate between non-inferiority and superiority VTE related death should be part of the primary efficacy outcome, whereas all-cause mortality should be included as the main safety outcome	Partly accepted. We have followed the same approach for selection of main efficacy endpoint in confirmatory studies in all VTE guidelines, including the VTE prophylaxis guideline in surgical patients (EMA/CHMP/41230/2015) and VTE treatment guideline (EMA/CHMP/325170/2012). The rationale is included in the VTE prophylaxis guideline in surgical patients (EMA/CHMP/41230/2015), which reads: "*The same clinically relevant events are recommended for superiority and for non-inferiority trials, except for causes of death. In non-inferiority trials, it is generally recommended to choose an endpoint reflecting as much as possible the effect of a drug; therefore, a VTE-related death (or a death considered to be due to VTE, such as*

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			fatal PE and sudden death, as autopsy findings may not be always available) is recommended as part of a composite endpoint. *For superiority trials, death from any cause is recommended as part of a composite endpoint*." We have rephrased the third paragraph of "confirmatory trials" subsection (in section 5.2. primary efficacy outcome) to keep consistency with the VTE prophylaxis guideline in surgical patients.
263 - 266	Comment 13 Stakeholder 1	Comment: The purpose of this text may be to explain the above, but is difficult to understand. In trials of this sort, where the distinction between efficacy and safety is blurred, one could argue that all-cause death is an efficacy end-point dependent on the objective of the trial. Regarding the distinction between non-inferiority and superiority trials we think that the guidance is eluding to the fact that data (and hence these endpoints) will be more 'noisy' if all cause death is used than if VTE-related deaths are. Typically you need less noisy data when conducting a non-inferiority trial, which is also the reason for treating the per-protocol analysis as the primary analysis in non-inferiority trials. We suggest that the inclusion of death in the composite endpoint is reconsidered. Furthermore, the discussions of analyses are missing in the part of competing risks. No single	Partly accepted. We have rephrased the said paragraph (third paragraph of "confirmatory trials" subsection included in section 5.2. primary efficacy outcome) to keep consistency with the VTE prophylaxis guideline in surgical patients. It is acknowledged that the cause of death cannot always be documented. That is why the guideline also includes that, in both cases, a supportive analysis of the composite endpoint should be provided using the alternative group of deaths i.e. VTE-related death for a superiority trial and all-cause death for a non-inferiority trial. Therefore, it is less restrictive than the proposed approach of

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		endpoint is more sensitive; as the cause of death cannot always be 'documented'. Instead the Grey/Wald tests should be used to account for the risk. It could be mentioned that competing risks are present in these types of trials and dependent on the population included and objective of the trial this should be considered/discussed when planning the analysis. From the guidance text it is assumed that a specific endpoint is not recommended (eg.: VTE yes/no or time to event).	simply discarding all-cause mortality among the composite efficacy endpoint for superiority. With respect to the type of statistical analysis to be conducted with the primary efficacy endpoint (e.g.: time-to-event, etc.) and additional analyses, they are considered in the appropriate "statistical considerations" subsection (in section 6.4: "Therapeutic confirmatory studies).
272 - 279	Comment 14 Stakeholder 1	Comment: **'**upper limb DVTs**'** As the underlying cause of upper and lower limb DVTs are different, the guideline should suggest separate analyses, in our opinion.	Accepted.
280	Comment 15 Stakeholder 1	Comment: **'**Diagnosis of symptomatic DVT or PE based solely on clinical signs and symptoms is discouraged.**'.** The guidance is suggested to be stricter: 'inadequate' rather than 'discouraged'. Proposed change (if any): Diagnosis of symptomatic DVT or PE based solely on clinical signs and symptoms is **inadequate**	Accepted. We have rephrased as follows: "...is ***inadequate and therefore it*** is discouraged".
284 - 287	Comment 16	Comment: With regard to rebound effect, further guidance is	Not accepted.

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	Stakeholder 1	needed to understand how to analyze data after discontinuation, i.e. during uncontrolled treatment. A primary analysis at end of treatment, and secondary analysis at 30 days could be suggested.	Further guidance is already included in Section 6.4 "Therapeutic confirmatory studies": a) in subsection "Design": *"An appropriate follow-up of at least 30 days after treatment discontinuation should be included to assess a possible rebound effect".* b) and in subsection "Statistical considerations": *'On-treatment' analyses and analyses including events occurring 7 days and 30 days after study drug discontinuation can be conducted in order to investigate a possible early rebound increase in thromboembolism after treatment cessation."*
286	Comment 17 Stakeholder 1	Comment: "…assessment o (e.g…." Proposed change (if any): delete "o"	Accepted.
402 - 421	Comment 18 Stakeholder 1	Comment: 'On-treatment' analyses are proposed, but that contradicts the recommended analysis 30 days after end of treatment Competing risk analysis is suggested. Guideline suggest time-to-event analysis for bleeding(safety), however this is not done for the efficacy analysis, consider to take this into account as appropriate	Not accepted. There is no contradiction in the text. As this is a general guideline, main potential basic scenarios are briefly mentioned. (i.e.: acute setting with on-treatment analysis and on-treatment plus 30 day post-treatment follow-up; long-term/chronic setting with time-to event analysis for the full duration of follow-up to end-of-study). Further statistical details are to be discussed on a case-by-case basis.

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486	Comment 19 Stakeholder 1	Comment: Inclusion of the bullet “clinically overt bleeding that necessitates surgical intervention” makes that it is wrongly stated in the guideline that the definition complies with the ISTH definition of major bleeding. In fact, in the publication of the ISTH definition it is stated” *Bleeding resulting in surgical intervention has not been included as a separate criterion as, if no other criteria for major bleeding have been satisfied, performance of surgical interventions will often be minor and not justify categorization as a major bleed.”* Proposed change (if any): One could potentially suggest to change this (take out the bullet) and instead include “clinically overt bleeding that does not meet the criteria for major bleeding but necessitates surgical intervention” under the definition for clinically relevant non-major bleeding (see also below comment).	Partly accepted. Major bleeding definition is a tricky issue. In fact, there are more than 15 different definitions available in the literature. The decision to operate or not can differ between one center and another. The same applies to blood transfusion, which is also a not purely objective criterion for major bleeding, as the decision to transfuse may differ between physicians and centers, but it is included in the ISTH definition as major bleeding criterion. In the end, it is the adjudicating committee of the study that has to decide centrally on the severity of the bleeding event based on the totality of the data. This is highlighted in the GL in the first paragraph of section 7.1, bleeding events. In deciding on the exact wording of the definition, it is important to be consistent with major bleeding definitions included in all revised CHMP guidelines and to keep consistency between major bleeding and life-threatening bleeding definitions (i.e.: as bleeding warranting surgical intervention for control is "life-threatening", according to many publications, it would be inconsistent to

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			qualify an event as life-threatening but not as major). On the other hand, it can be discussed whether a minor surgery to drain a superficial bleeding should be used as sole criterion to adjudicate the bleeding as major. In line with the BARC Consensus document, those "minor surgeries" to drain a skin hematoma, or to control dental, nasal or hemorrhoid bleeding should not be used as sole criterion to qualify a bleeding as warranting surgery to control bleed (Mehran et al. *Circulation*. 2011; 123: 2736-47). Therefore, it has been clarified in the text that the criterion of "bleeding warranting surgical intervention for control" does not apply to dental/nasal/skin/hemorrhoidal bleeding, supported by a reference to the BARC consensus (new reference nr. 26).
504	Comment 20 Stakeholder 1	Comment: Given the above cited sentence from the ISTH recommendation it seems better to have “surgical intervention” alone as part of the definition for life-threatening bleeding.	Not accepted. If a bleeding qualified as "life-threatening", like those requiring surgery to control bleeding, there is no reason to exclude it from the assessment of major bleedings.

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		Proposed change (if any): Delete “Necessitated surgical intervention.”	
506 - 511	Comment 21 Stakeholder 1	Comment: Suggested addition in bold – if decided to exclude the text suggested under major bleeding (see above comments). Proposed change (if any): Clinically relevant non-major bleeding [24,26] is defined as any clinically overt bleeding that does not meet the criteria for major bleeding but requires **surgical intervention,** medical attention (e.g.: hospitalisation, medical treatment for bleeding) and/or a change in antithrombotic therapy (including discontinuation or down- titration of study drug) and/or any other bleeding type considered to have clinical consequences for a patient.	Partly accepted. The proposal of re-classifying all bleedings requiring surgical intervention among non-major bleedings is not endorsed . The inclusion of surgical intervention as criterion for major bleeding is well supported by many studies, scales and consensus documents, like those used in RE-LY, PLATO, CURE, CURRENT-OASIS 7, STEEPLE, and BARC initiative (Type 3b bleeding). However, in accordance with answer to comment 19, it has been clarified in the text that the criterion of "bleeding warranting surgical intervention for control" does not apply to dental/nasal/skin/hemorrhoidal bleeding, supported by a reference to the BARC consensus. It is implicit that those bleedings not fulfilling major bleeding criteria (e.g.: minor surgery for control of dental/ nasal/ skin/ hemorrhoidal bleeding not associated with a

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			decrease in the haemoglobin level of more than 2 g/dL and not leading to transfusion of two or more units of whole blood or packed cells), will have to be included as clinically relevant non-major.
523 - 530	Comment 22 Stakeholder 1	Comment: It is not completely clear what the aim of the endpoints listed is and how to combine them - and if these endpoints could be included or if they should be included? If the latter is true it will be a lot of secondary end-points to include in a study.	Not accepted. The guideline specifies that "*the adjudication of bleeding events by a central independent and blinded committee of experts, using pre-specified limits and clear terms of reference is strongly encouraged".* The guideline includes a list of examples of bleedings that may be considered as "clinically relevant non-major". Ultimately, the adjudication committee is responsible for deciding if the bleeding event fulfils at least one of the criteria of major bleeding and, if negative, if it may be considered as "clinically relevant non-major". It is expected that the protocol designs would allow for a description of bleeding events by localisation, as requested in the guideline and as provided in the clinical study reports of all contemporary studies conducted with new antithrombotics, but it is not expected to plan a statistical analysis of each type of clinically-

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			relevant bleeding by specific localisation as separate endpoint.