21 May 2013
EMA/CHMP/47495/2013
Committee for Medicinal Products for Human Use (CHMP)

Overview of comments received on 'Guideline on clinical investigation of medicinal products for prophylaxis of high intra- and post-operative venous thromboembolic risk (EMA/CHMP/325170/2012) (former CPMP/EWP/707/98 Rev.1 corr.)

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

Stakeholder no.	Name of organisation or individual
1	EFPIA
2	SciencePharma Ltd., Limited Joint-Stock Partnership

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1. General comments – overview

Stakeholder no.	General comment (if any)	Outcome (if applicable)
1	There are a couple of section of the draft guideline that if retained could jeopardise clinical development in this indication (see comments on 274-277 and 376 – 377)	Not agreed. This review of the guideline is focused on standardisation of safety endpoints definitions and methods for assessment. Therefore, compared with previous version, it does not change the main requirements to shown non-inferiority and it does not change any parameter that would require higher sample sizes, additional studies, additional tests or additional follow-up not usually conducted in standard clinical practise.

2. Specific comments on text

Line no.	Stakeholder no.	Comment and rationale; proposed changes	Outcome
77-78	1	Comment: • Need to clarify here that the only risk being discussed (stratified) here is related to the surgery and not to other conditions that the patient may have. Proposed change (if any): • The risk stratification to three (high-moderate-low) **surgery-related** VTE risk levels allows for the implementation of group-specific VTE prophylaxis at each risk level:	Accepted.
86-88	1	Comment: • The guidance states, "Therefore, it is recommended that a sufficient number of patients with high surgery-related VTE risk level and with intrinsic risk factors for VTE (i.e. age, cardiac disease, infection/inflammation, cancer other than that to be operated), be evaluated in clinical trials in order to permit an adequate benefit / risk assessment at the optimal dose of the drug in these sub-populations due to the heterogeneous nature of VTE predisposing	Not accepted. The proposed statement is already included in section 4.1.1: *"Therefore, it is recommended that **a sufficient number of patients … with intrinsic risk factors for VTE (i.e. age, cardiac disease, infection/inflammation, cancer other than that to be operated)**, be evaluated in clinical trials in order to permit an adequate benefit / risk assessment at the optimal dose of the drug in these sub-populations due to the heterogeneous nature of VTE predisposing factors."*

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		factors." • It is true clinically that the VTE risk from the surgery should be considered above the risks related to the patients' risk factors as many patients without obvious other risks develop VTE following those procedures that is incompletely mitigated by use of prophylactic measures. Surgical and patient-related risks are however, at least additive and more likely, multiplicative when combined. The text in line 155 is true that excluding patients with patient-related risks would not reflect reality. Including a minimum percentage of patients with intrinsic risks would be more relevant to clinical practice than if they were excluded or if few were included. Proposed change (if any): • To the end of the sentence add "It is recommended that a minimum percentage of patients with intrinsic risks are included in the study."	
140	1	Comment: • Regarding "treatment for cancer (e.g. prostate cancer)" as risk factors for VTE, it would be better to indicate examples of cancer treatment	Partly accepted. Other therapies for cancer, apart from surgery, such as chemotherapy, placement of central venous catheters, radiotherapy, hormonal manipulation (eg., tamoxifen),

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		drugs rather than cancer types. Please specify if text refers to hormonal therapy for prostate cancer? What about myeloma treatments?	angiogenesis inhibitors (e.g., bevacizumab, thalidomide, lenalidomide) and supportive therapies (i.e., steroids, blood transfusion, white blood cell growth factors and erythropoiesis-stimulating agents), may increase the risk of VTE. However, it is not the objective of the revision to specify all potential treatments for cancer that may increase the risk of VTE. Therefore, we have shortened the phrase corresponding to “cancer” as VTE risk.
152	1	Comment: • “small” weight should be “low” weight Proposed change (if any): • “low weight”	Accepted.
156 - 161	1	Comment: • The guideline is requesting that a “sufficient” number of patients be included to allow and “adequate benefit/risk assessment. This is seen as critical as these trials are powered for the overall patient population included. • The guidance states, “Therefore, it is recommended that a sufficient number of patients with high surgery-related VTE risk level and with intrinsic risk factors for VTE (i.e. age, cardiac disease, infection/inflammation, cancer	Accepted.

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		other than that to be operated), be evaluated in clinical trials in order to permit an adequate benefit / risk assessment at the optimal dose of the drug in these sub-populations due to the heterogeneous nature of VTE predisposing factors." This statement seems to be discordant with the statement in lines 86-88 which seems to discount the intrinsic risks and, therefore, considers the populations to be homogeneous as long as they all have high risk surgery (as defined herein). Proposed change (if any): • Therefore, it is recommended that ~~a sufficient number of~~ patients with high surgery-related VTE risk level and with intrinsic risk factors for VTE (i.e. age, cardiac disease, infection/inflammation, cancer ~~other than that to be operated~~), be evaluated in clinical trials in order to permit an adequate benefit / risk assessment at the optimal dose of the drug in these sub-populations due to the heterogeneous nature of VTE predisposing factors. Benefit/risk assessment in these sub-populations should be consistent with the overall results.	
169	1	Comment:	Accepted.

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		• No consistent risk of VTE with cemented vs. cementless prosthesis has been proven in prior trials. Proposed change (if any): • Remove from sentence.	The example of cementation of the prothesis as confounding factor may be deleted from the guideline.
189	1	Comment: • NSAID interruption is under the control of the orthopaedic surgeon, not the clinical trialist. • Recommend to delete the last sentence starting on line 191.	Not accepted. The guideline already acknowledges that NSAID interruption or maintenance is a matter of clinical practise and therefore only includes a recommendation about keeping on NSAID as much as possible in spite of the possible increase in side effects.
194-196	1	Comment: • The guidance states, “DVT may be diagnosed by bilateral ascending contrast venography, duplex ultrasound or colour duplex ultrasound.” • CT venography is sometimes combined with CT angiography of the chest in the assessment of PE and in PIOPED II was shown to have similar sensitivity/specificity to ultrasound (goodman AJR 2007). It proposed therefore that the guideline is expanded to reference CT venography as a diagnostic tool.	Not accepted. The inclusion of CT venography as a diagnostic tool is outside the scope of this review. In addition, data available are very limited in thromboprophylaxis trials.

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		Proposed change (if any): • DVT may be diagnosed by bilateral ascending contrast venography, duplex ultrasound or colour duplex ultrasound, or CT venography.	
274-277	1	Comment: • The requirement to perform at least one confirmatory trial with an efficacy endpoint excluding asymptomatic distal DVTs means the end of clinical development in this indication due to the very high number of patients needed.	Not accepted. This is not a new requirement; it was already discussed in previous guideline and is outside of the scope of current revision.
282	1	Comment: • Please define “total DVT”, i.e. is it symptomatic and asymptomatic events? If venographies are systematically performed as recommended, it is likely that some patients will be treated for asymptomatic distal DVT after being withdrawn from study treatment. This will include a bias.	Partly accepted. A clarification has been included in the text of the guideline: “(symptomatic and asymptomatic””. At the end of section 4.3.1 is stated that: “Normally, screening tests for diagnosing asymptomatic DVT and/or PE should be performed within 24 hours after the last dose of study treatment, or earlier if patient develops symptoms during study treatment.” Therefore, the unavoidable potential bias would occur outside the time of primary assessment of the main outcome (after venography).
285	1	Comment:	Accepted.

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		• Please define “Incidence of PE”, i.e. is this fatal and non fatal or only non fatal if fatal PE is counted in the VTE-related deaths?	It refers to “symptomatic non-fatal PE”, as fatal PE is already included in the VTE-related deaths
288	1	Comment: • Incidence of VTE during follow-up: it is a problem to adjudicate VTE after end of study treatment as patients are outpatients etc…	Not accepted. The problem is acknowledged, but it does not preclude for not assessing post-treatment VTE.
289	1	Comment: • “… standardized as completely as possible and treated…”: it is not clear what “standardized” and “treated” mean – the latter could imply pharmacologic intervention. Furthermore, the care of the patient within the follow-up period after trial drug discontinuation is almost never under the complete direction of the orthopaedic surgeon, but rather rehabilitation, family, and local doctors. Standardization is not likely due to differences in regional care. The guideline could be reworded to reflect this Proposed change (if any): • Consider replacing “treated” by “handled.” • Incidence of VTE (PE and/or DVT) within a follow-up period after trial drug discontinuation, usually 4 to 6 weeks, standardised as	Accepted.

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		completely as possible~~, and treated in a comparable way in all treatment arms of the trial~~.	
300	1	Comment: • "… safety profiles (bleeding)…" should add "and VTE risks"	Accepted.
318	1	Comment: • "hip replacement and hip fracture together": It is not easy to include in one single study patients with a planned surgery and a surgery in emergency.	Partly accepted. The intention of current wording is not to ask for a single study with hip replacement and hip fracture patients together. The intention of the wording is that, for a claim of a broad indication in "major orthopaedic surgery", positive data of both hip replacement and hip fracture have to be submitted. These data may be generated in a single pivotal trial with stratification depending on the type of surgery, or in separate trials. The wording has been slightly modified for clarity.
339	1	Comment: • Please define what is meant by "if properly justified"; examples would be helpful.	Not accepted. This guideline is a general document. Specific cases should be analysed in a case by case basis.
355	1	Comment and Proposal: • A follow-up of 3 months is very long and difficult to perform in real life. Therefore,	Not accepted. A 90 day follow-up has been conducted in contemporary trials in this indication (e.g.: RE-NOVATE, RE-MODEL, RE-

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		although the text currently reads “usually 3 months”, we would suggest to delete it and leave only “at least 1 month” Proposed change (if any): • “Safety outcomes should be assessed separately on-treatment and during follow-up (at least 1 month; ~~usually 3 months~~).”	MOBILIZE, ADVANCE 1-3). There are important safety issues (rebound thromboembolism, functional outcomes) that would require a 3-month follow-up to be assessed.
361	1	Comment: • Some potentially useful coagulation tests have been overlooked. Proposed change (if any): • Chromogenic Factor Xa-based assays should be included. PT may have value with certain new oral anticoagulants in development.	Partly accepted. It is not the intention of the guideline to provide with a comprehensive list of all potential coagulation tests that may be applicable for any new type of antithrombotic. Therefore, only general coagulation tests have been included. We have now included a reference to PT, given that it is a general coagulation test, as well as a reference to any other coagulation test that may be relevant for specific products. It is understood that this latter general statement would comprise chromogenic factor Xa-based assays for factor-Xa inhibitors or plasma-diluted thrombin time for direct thrombin inhibitors or any other specific coagulation assay developed in the future.
371	1	Comment: • “Impaired liver function”: Please clarify if in healthy volunteers or in patients. • “impaired liver function” – please provide	Not accepted. The requested guidance is outside the scope of this review. Please refer to section 3 of the guideline: “This guideline should be read in conjunction with the introduction and

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		guidance on the definition. Unfortunately, assessment of liver function cannot be quantitated in a simple lab test or number. The results of the various tests that can be performed may vary considerably as they assess different hepatic functions. SmPCs/Labels reference use of the Child system with Pugh modification. Child Pugh is not routinely assessed in patients but rather used as a determinant for the assessment of the severity and prognosis of chronic liver disease, primarily cirrhosis, and specifically whether such patients are candidates for liver transplantation. • Obese – please provide some definition for guidance (e.g. by weight or BMI?).	general principles of the Annex I to the Directive 2001/83/EC as amended, and other pertinent elements outlined in the current and future EU and ICH guidelines and regulations"
376-377	1	Comment: • The development of new medicinal products for VTE prophylaxis in high risk surgery patients is further jeopardized by the recommendation to perform an "open dose-ranging study" before implementation of the major dose-finding studies, is unrealistic and will trigger complications and delays in development. delays.	Not accepted. This is not a new requirement; it was already discussed in previous guideline and is outside of the scope of current revision.

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381	1	Comment: • Line 381 recommends a double-blind design – please clarify what exactly is meant.	Not accepted. We think the mentioned phrase is sufficiently clear and does not need modification: “Randomised, parallel group, double-blind design is recommended.”
398	1	Comment and Proposal: • The use of placebo is definitely unethical in patients at high risk of VTE. Proposed change (if any): • “In patients at high risk of VTE, the use of placebo ~~may be~~ *is* unethical and therefore it is not recommended.”	Not accepted. There are some situations in which the use of thromboprophylaxis is not established, like in extension of thromboprophylaxis in knee replacement. In these situations, the use of placebo may be ethical. Therefore, it is not appropriate to be categorical in this statement.
412	1	Comment: • “reasonable representation”: Please define/specify what “reasonable” means.	Partly accepted. Reasonable representation means a representative number.
420, 447, 456, 463, 477, 478, 498	1	Comment: • The use of the term “bleeds” is colloquial. Proposed change (if any): • Use the term “bleeding event” in place of “bleeds”	Accepted.
437	1	Comment:	Not accepted.

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		• "Clinically overt bleeding": Please provide a definition for "overt"	The term "clinically overt" is equivalent to clinically evident (evident signs of bleeding) and broadly used in the medical literature. Therefore, a clarification is not deemed necessary in the text.
493-496	1	Comment: • Please clarify the apparent inconsistency in the timing and duration of assessment of bleeding events as specified in lines 354-355 (which discusses timing of safety assessments) versus 493-496 (which discusses collection of bleeding events), i.e. "during follow-up (at least 1 month; ...)" versus "until (...) study drugs have been cleared from plasma", respectively.	Not accepted. There is no discrepancy between the mentioned sections. Bleeding events are usually assessed on-treatment, while overall safety is assessed during treatment and follow-up.
458	1	Comment: • "Fatal, symptomatic intracranial bleed" is not just life-threatening, it is life-ending. Please clarify of "Non-fatal" means "symptomatic intracranial bleed"	Accepted. It is acknowledged that the first item is ambiguous: "Fatal, symptomatic intracranial bleed". Therefore, it has been re-phrased as follows: "- Fatal bleeding; - non-fatal intracranial bleeding".
462	1	Comment: • Draining or puncture of a haematoma at the surgical site, in the operating theatre or at the besides seldom of as much significance as an ICH.	Not accepted. "Necessitated surgical intervention" is among the criteria of life-threatening (references 13, 14)

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		Proposed change (if any): • Remove from “Life-threatening”	
497	1	Comment: • Has input been solicited through discussion with a panel of orthopaedic surgeons to verify and gain knowledge about surgical practice. It is strongly recommended.	Not accepted. The need for standardisation of the different bleeding-related parameters already included in contemporary VTE orthopaedic surgery trials is widely recognised in the literature among orthopaedic surgeons and anesthesiologists (Dahl et al, J Thromb Haemost 2010; 8: 1966–75; Rosencher et al: J Thromb Haemost 2010; 8: 1442–3.).
500	1	Comment: • There is a typographical error relating to the plasma haemoglobin level. Proposed change (if any): • From “haemoglobin plasma level” to plasma haemoglobin level.”	Accepted.
500	1	Comment: • “red cell count changes”: please explain the rationale.	Not accepted. The red blood cell count is almost always part of the standard complete blood count test and can help diagnose anemia, usually due to bleeding in the case of antithrombotics. It is not accepted to extend the text of the guideline with obvious explanations.

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502 - 505	1	Comment: • The number, type, and manufacturer swabs, drapes and suction bottles varies around the world, as does their use by surgeon. Assessment of operative blood loss can be difficult to perform and is unlikely to be helpful as the data are unreliable and will likely lead to false conclusions. This could be verified through discussion with orthopaedic surgeons Proposed change (if any): • Remove	Not accepted. Blood loss through drainages has already been included as secondary safety endpoint in contemporary trials. Although the difficulties for collecting blood loss are acknowledged, this does not prevent to its inclusion as secondary endpoints in orthopaedic thromboprophylaxis trials, as blood loss is clinically relevant. This issue has been repeatedly verified in different methodological reviews.
504	1	Comment: • Typographical error: "...quantified by and objective method..." Proposed change (if any): • "...quantified by an objective method..."	Accepted.
507-511	1	Comment: • The formula to calculate blood loss seems very cumbersome and unrealistic to be requested for a clinical trial.	Not accepted. It is only a matter of collection of data input. The calculation is a simple formula that can be done automatically with an excel sheet. The 2008 EMA guideline already recommended the use of this formula for the blood loss calculation as a safety criterion. This has to be applied for phase 2 and 3 studies. Therefore, rather than modifying criteria from one

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			study to another, physicians conducting clinical trials should follow this European recommendation [Rosencher et al: J Thromb Haemost 2010; 8: 1442–3].
509-510	1	Comment: • Has this value of 150 ml per RBC or cell saver unit been validated and agreed upon by anaesthesiologists and surgeons?	Not accepted. This value and formula was proposed by anaesthesiologists and agreed in the 2008 EMA guideline.
512	1	Comment: • It needs to be clear which “Bleeding Index” is being used, and to ensure that it is validated. This is the original Bleeding Index from 1989 by Landefeld *et al.* and using whole units of blood transfused is too gross a measure to be reliable or accurate.	Not accepted. The guideline already gives a definition of Bleeding index (BI), which is based on the one used in the fondaparinux trials, but not limited to a bleeding episode. Bleeding index can be considered an objective measure of blood loss [Dahl et al, J Thromb Haemost 2010; 8: 1966–75]. Some investigators have questioned the importance to patients of surgical blood loss and bleeding index. However, an individual patient meta-analysis involving 13 085 patients in eight phase three randomized controlled trials comparing fondaparinux with control for the prevention of VTE that major bleeding defined, at least in part, by a bleeding index of at least two was associated with a sevenfold increased risk of death [Eikelboom et al. Circulation 2009; 120: 2006–11]. Therefore, its inclusion as a secondary safety endpoint as objective measure of blood loss is justified.

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517	1	Comment: • Autologously collected blood can only be given to the patient who donated it. Surgeons do not want to discard it, and so often it is given to the patient if it is safe to do so, even if it is not clinically needed.	Accepted.
519	1	Comment: • The volume of blood (ml) in each bag varies, and very often the amount in each bag is not collected in the operating room, as opposed to just counting the number of units of blood given.	Accepted.
523	1	Comment: • "It is encouraged the collection…." Grammatical error here – do we mean "The collection of the number and percentage of patients with wound complications in the safety population is to be encouraged?"	Accepted.
527	1	Comment: • Clarification is sought on whether time to complete wound healing could be determined as "considered healed at visit N. Complete healing will occur outside of the hospital, and it would be impractical to determine on which day	Accepted.

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		"complete wound healing" occurs.	
543	1	Comment: • Please define "cardiovascular deaths"	Accepted. Now included in section "Definition of terms".
Lines 181-184	2	Comment: These statements suggest that although aspirin and other antiplatelet drugs are effective at reducing major vascular events in patients with atherosclerotic disease, e.g. myocardial infarction, only aspirin treatment is clearly allowed to be continued in patients with risk of major vascular events in spite of increased risk of bleeding. No recommendations are given if other antiplatelet drugs could be continued in these patients and it is not clear if an intention is to allow treatment only with aspirin, or with other than aspirin oral antiplatelet drugs as well. Such recommendations for a group of oral antiplatelet drugs and not only aspirin would be very welcome, as these drugs are commonly used for long-term treatment as separate therapy (including cases when aspirin is not tolerated) or in combination with aspirin. The proposed change has been prepared assuming that oral antiplatelet therapy is not expected to be interrupted as a rule in high-VTE risk surgery trials. Proposed change (if any): "However, aspirin and other antiplatelet drugs are	Accepted.

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		effective at reducing major vascular events in patients with atherosclerotic disease, e.g. myocardial infarction. Therefore, it is not necessary that aspirin **oral antiplatelet drugs** be interrupted in patients with risk for major vascular events in spite of increased risk for bleeding."	
Lines 184-186	2	Comment: Not all of oral antiplatelet drugs can inhibit platelet function for their lifespan (which is estimated to be 7-10 days). It is characteristic for both aspirin and irreversible ADP P2Y receptors inhibitors, while dipyridamol reversibly inhibits platelet aggregation by a mechanism leading to elevation of platelet cAMP levels. Moreover, the antiplatelet effect of oral antiplatelet drugs that irreversibly inhibit aggregation does not last precisely a week, as after they are interrupted new platelets are continuously produced to restore clinically proper aggregation often within less than 7 days. The change has been proposed to improve an accuracy of the text: Proposed change (if any): "Stopping aspirin **oral antiplatelet drugs** in such patients immediately prior to surgery will not reduce peri-operative bleeding (because **their** antiplatelet	Accepted.

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		effect lasts usually about a week)."	
Lines 186-188	2	Comment: Considering dipyridamol mechanism of action and to provide for a possibility of future new oral drugs with reversible antiplatelet effect development, the change in the last part of the paragraph under discussion has been proposed. Proposed change (if any): "If necessary, aspirin **oral antiplatelet drugs** might be interrupted in patients with very high bleeding risk **and/or in patients taking drugs producing reversible antiplatelet effect**. This remains at the discretion of the physician. It is important to ensure that aspirin oral antiplatelet drugs be re-prescribed after surgery."	Accepted.