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Committee for Medicinal Products for Human Use (CHMP)

Concept paper on the need for revision of the guideline on clinical investigation of medicinal products for prophylaxis of high intra- and post-operative venous thromboembolic risk (CPMP/EWP/707/98 Rev.1 corr.)

Draft

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Comments should be provided using this [template](#). The completed comments form should be sent to CVSWPSecretariat@ema.europa.eu

Keywords	<i>Venous thromboembolism, prophylaxis, major bleeding, guidelines, anticoagulant, CHMP</i>
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1. Introduction

A key element in the benefit risk assessment of drugs used for prophylaxis of venous thromboembolism (VTE) is balancing their antithrombotic effect versus the risk of bleeding. The high variability in the assessment and reporting of bleedings, perioperative blood loss and transfusions in orthopaedic VTE prevention trials has the potential to impact the interpretation of results of individual randomized controlled trials and, ultimately, makes difficult the benefit-risk assessment of new antithrombotics.

2. Problem statement

Despite repeated calls for standardization of the assessment and reporting of bleeding and proposals for a standardized definition by the European Medicines Agency (EMA) [CPMP/EWP/707/98 Rev.1 corr.] and other organizations, there has been a high variability in the assessment and reporting of bleedings, perioperative blood loss and transfusions in orthopaedic VTE prevention trials. Such variability has the potential to impact the interpretation of results of individual randomized controlled trials, can lead to a significant infraestimation of bleeding potential in some cases and complicates the comparison of bleeding rates across trials [Dahl et al, 2010; Hull et al, 2009].

In 2000 the EMA recommended the inclusion of fatal bleeding; clinically overt bleeding causing a fall in haemoglobin level of 2 g/dL or more; clinically overt bleeding leading to transfusion of two or more units of packed cells or whole blood; retroperitoneal or intracranial bleeding; or bleeding warranting treatment cessation in the definition of major bleeding for VTE prevention trials [CPMP/EWP/707/98]. This definition was updated in 2007 to include bleeding leading to treatment cessation, occurring at the surgical-site and leading to re-operation or to any unusual medical intervention [CPMP/EWP/707/98 Rev.1 corr.]. The revised guideline also recommended the use of objective blood loss calculation as a safety criterion. This had to be applied for phase 2 and 3 studies.

The International Society of Thrombosis and Haemostasis (ISTH) recommendations for the reporting of major bleeding events for non-surgical patients [Schulman et al, 2005] included a description of bleeding into critical organs while excluding bleeding leading to treatment cessation [Schulman et al, 2005]. The International Surgical Thrombosis Forum (ISTF) in 2008 recommended that surgical bleeding should be objectively measured and other clinical bleeding events should be adjudicated and categorized by severity [Dahl et al, 2008]. The ISTH has recently proposed a standardised definition of major bleeding in surgical patients [Schulman et al, 2010]. It has been criticised, mainly because it includes subjective assessment of the amount of bleeding during the procedure [Rosencher et al, 2010].

Definition and categorisation of bleeding events is of critical importance in the establishment of the benefit/risk conclusion of new antithrombotics. The use of the different definitions mentioned above on the same data set could have a major impact on the B/R conclusion. Therefore, there is a need to discuss established criteria, using conservative definitions that can be used as a reference for the assessment of each individual product and as a tool to conduct comparative exercises between studies.

Additionally, the potential impact of the type of thromboprophylaxis in functional and surgical outcomes also deserves investigation in VTE thromboprophylaxis trials [AAOS, 2007; Rosencher et al, 2010]. The Harris Hip (HH) Score [Harris, 1969] and the Knee Society (KS) score [Insall et al, 1989] are clinician completed functional scores available for use in orthopaedic surgery.

Arterial thromboembolic events (ATE) such as stroke and acute coronary syndromes, are important adverse events following orthopaedic surgery [Lanes et al, 2011]. Secondary combined efficacy and safety endpoints may help to assess the net clinical benefit of new thromboprophylactic regimes.

3. Discussion

The following critical aspects will need to be discussed and covered as appropriate by the revised guideline:

1. Inclusion of clarifications to the current definition of major bleeding and its assessment, in order to provide an objective and standardised definition of major bleeding as well as a detailed description of methods for measuring blood loss associated to a major bleed and timing for collection of data.
2. To provide a definition of clinically relevant minor bleeding.
3. To update list of secondary endpoints related to the reporting of surgical blood loss, blood transfusions and surgical wound outcomes (i.e: time to wound healing, wound infections).
4. To include additional secondary safety outcomes of clinical importance for new anticoagulants, like hepatic events or arterial thromboembolism.
5. Discuss the need and value of including functional outcomes as secondary efficacy endpoints in pivotal trials and to make proposals accordingly.
6. Pertinence of the inclusion of secondary combined efficacy and safety clinical endpoints.

All pertinent elements outlined in current and future EU and ICH guidelines and regulations should also be taken into account.

4. Recommendation

The Cardiovascular Working Party/CHMP recommends revising the Guideline on Clinical Investigation of Medicinal Products for Prophylaxis of Intra- and Postoperative Venous Thromboembolic Risk [EMA/CHMP/EWP/707/98 rev 1]. The revised guideline will include clarifications to the current definition of major bleeding and assessment, as well as detailed methods for measuring blood loss associated to a major bleed and timing for collection of data. The revised guideline is also intended to include a definition of clinically relevant minor bleeding and other secondary safety outcomes, functional outcomes and secondary combined efficacy and safety endpoints.

5. Proposed timetable

It is anticipated that a draft document may be agreed by the CVWP in May 2011. The draft may be adopted by the CHMP for release for consultation in June 2011. The draft document will then be released for 3 months of external consultation and following the receipt of comments it will be finalised within approximately 3 months.

6. Resource requirements for preparation

The drafting process will be done in close relationship with the BPWP. An expert meeting may be needed depending on the difficulties encountered during the drafting process.

7. Impact assessment (anticipated)

The document is intended to clarify methodological aspects, mainly related to bleeding events and secondary safety endpoints, when performing trials to develop drugs for prophylaxis of high intra- and post-operative venous thromboembolic risk. It should also provide a clear basis for the CHMP when assessing primary safety data and secondary efficacy and safety data of clinical relevance from studies for antithrombotic drugs in this indication and providing advice in this field.

8. Interested parties

The interested parties in the guideline include the industry (PhARMA, EFPIA, JPMA and others), Academia, The European Federation of National Associations of Orthopaedics and Traumatology (EFORT), The International Surgical Thrombosis Forum (ISTF), The International Society of Thrombosis and Haemostasis (ISTH), European Society for Cardiology (ESC), Société Française D'anesthésie et de Réanimation (SFAR), clinical trialists in VTE and other Regulatory Agencies.

9. References

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