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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 the prophylaxis of venous thromboembolic risk in non-surgical patients (CPMP/EWP/6235/04)

Agreed by Cardiovascular Working Party	26 March 2014
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Comments should be provided using this template. The completed comments form should be sent to CVSWPSecretariat@ema.europa.eu

Keywords	**Venous thromboembolism, prophylaxis, major bleeding, guidelines, anticoagulant, CHMP**

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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. Since the publication of the CHMP guidance on clinical investigation of medicinal products for the prophylaxis of venous thromboembolic disease [CPMP/EWP/6235/04] in 2006 [1], a number of new EMA guidelines related to clinical investigation with antithrombotics have been released [2,3] or are being revised [4]. An update of the CPMP/EWP/6235/04 guideline on non-surgical patients, particularly related to the assessment of safety and bleeding events, is considered necessary to adapt its content to current scientific knowledge and to harmonise it with the content of the new or revised EMA guidelines related to clinical investigation with antithrombotics.

2. Problem statement

Definition and categorisation of bleeding events is of critical importance in the establishment of the benefit/risk conclusion of new antithrombotics. Recently, the EMA guidelines on VTE prophylaxis in high-VTE risk surgery [EMA/CHMP/325170/2012] [2] and the EMA guidelines on prevention of stroke and systemic embolism in non-valvular atrial fibrillation (AF) [EMA/CHMP/450916/2012] [3] have included harmonised bleeding definitions and recommendations about collection and assessment of bleeding events. Additionally, harmonised additional secondary safety outcomes of clinical importance for new antithrombotics, like hepatic events or arterial thromboembolism, were included. Therefore, the harmonisation regarding these aspects has to be extended to the revised Guideline for prophylaxis of VTE in non-surgical patients [CPMP/EWP/6235/04] [1].

On the other hand, medical patients have a significantly heterogeneous risk for VTE.

Therefore, prophylaxis of VTE may differ in particular situations or populations [5]. The need for pharmacological thromboprophylaxis is usually limited to those patients at high risk of VTE (e.g.: acutely ill non-surgical patients with additional risk factors) and only during the period of risk (e.g.: during the period of patients immobilization or acute hospital stay) [5]. Specific recommendations, requirements and/or dedicated studies may be needed depending on the claimed indication and treatment duration (e.g.: acute versus extended prophylaxis) and target population (e.g.: acutely ill non-surgical patients at high risk of VTE, outpatients with cancer, etc.). As a result, active drugs or placebo may be suitable as control in comparative trials, depending on VTE risk of the included population and period of risk.

Finally, despite venography is the gold standard for diagnosis of DVT [1], recent trials have used bilateral compression ultrasonography (CIS) for the detection of DVT, mainly because it is a non-invasive method and has a good sensitivity and specificity in detecting proximal DVT.

3. Discussion (on the problem statement)

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

1. Updated definition of bleeding events (e.g.: major bleeding and clinically relevant non-major bleeding) and its assessment, according to recent CHMP guidelines, in order to provide an objective and standardised definition of bleedings as well as a detailed description of methods for measuring blood loss and timing for collection of data.

2. Inclusion of additional secondary safety outcomes of clinical importance for new antithrombotics, like hepatic events or arterial thromboembolism.

3. Discussion on the need for dedicated studies depending on the claimed indication, target population (e.g.: acutely ill non-surgical patients at high risk of VTE, outpatients with cancer, etc.) and treatment duration (e.g.: acute versus extended prophylaxis).

4. Clarifications regarding imaging tests to be used in dose-finding and confirmatory trials.

4. Recommendation

The Cardiovascular (CVS) Working Party/CHMP recommends revising the Guideline on Clinical Investigation of Medicinal Products for the prophylaxis of venous thromboembolic risk in non-surgical patients [EMEA/CPMP/EWP/6235/04]. The revised guideline will include an update of several methodological issues related to the prophylaxis of VTE, as described in previous section.

5. Proposed timetable

This CP is released for 3 months public consultation. Following this it is planned to release the draft Guideline within 6 months after the completion of the public consultation on the CP. The draft Guideline will be released for 6 months public consultation and following the receipt of comments it will be finalised within approximately 6 months.

6. Resource requirements for preparation

The drafting process will be done internally at the CVS WP. An expert meeting may be needed depending on the difficulties encountered during the drafting process.

7. Impact assessment (anticipated)

The document is intended to update methodological aspects when performing trials to develop medicinal products for the prophylaxis of VTE in non-surgical patients. 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 medicinal products in this indication and providing advice in this field.

8. Interested parties

The interested parties in the guideline include the Industry, Academia, The International Society of Thrombosis and Haemostasis (ISTH), European Hematology Association (EHA), European Society for Cardiology (ESC), European Federation of Internal Medicine (EFIM), European Society for Vascular Surgery (ESVS), European Society of Radiology (ESR) and clinical trialists in VTE.

9. References to literature, guidelines, etc.

1. Committee for Medicinal Products for Human Use (CHMP). Guideline on clinical investigation of medicinal products for the prophylaxis of venous thromboembolic risk in non-surgical patients. CPMP/EWP/6235/04. London, 1 June 2006.

2. Committee for Medicinal Products for Human Use (CHMP). Guideline on clinical investigation of medicinal products for prevention of venous thromboembolism (VTE) in patients undergoing high VTE-risk surgery. EMA/CHMP/325170/2012 (former CPMP/EWP/707/98 Rev. 2 corr). London, 30 May 2013

3. Committee for Medicinal Products for Human Use (CHMP). Guideline on clinical investigation of medicinal products for prevention of stroke and systemic embolic events in patients with non-valvular atrial fibrillation. EMA/CHMP/450916/2012. Draft.

4. Draft concept paper on the need for revision of the guideline on clinical investigation of medicinal products for the treatment of venous thromboembolic disease. EMA/CHMP/281099/2013. London, 30 may 2013.

5. Kahn SR, Lim W, Dunn AS, Cushman M, Dentali F, Akl EA, et al; American College of Chest Physicians. Prevention of VTE in nonsurgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012; 141(2 Suppl): e195S-226S.