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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 treatment of venous thromboembolic disease (CPMP/EWP/563/98)

Agreed by Cardiovascular Working Party	27 March 2013
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Start of public consultation	03 June 2013
End of consultation (deadline for comments)	01 September 2013

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

Since the publication of the *EMA Guideline on clinical investigation of medicinal products for the treatment of venous thromboembolic disease [CPMP/EWP/563/98]* in 2000, there has been an intense research in this field. An update of the mentioned guideline is considered necessary to adapt its content to current scientific knowledge and to harmonise it with the content of new or revised EMA guidelines related to clinical investigation with antithrombotics.

2. Problem statement

During the last decade, a number of new studies on the treatment of venous thromboembolism (VTE) have been conducted. Some of them have served for new compounds to obtain the indications of treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) (e.g.: fondaparinux, rivaroxaban) and treatment of spontaneous superficial vein thrombosis (SVT) (e.g.: fondaparinux).

Current clinical practice guidelines make a distinction between acute treatment (usually first 7 days), long-term treatment (from day 7 to 3 months) and extended treatment of VTE (from 3 months to indefinite), as well as between treatment of DVT and SVT [Keaton et al, 2012]. In addition, the management of VTE may differ in particular situations or populations [e.g.: VTE associated to cancer, central venous catheters (CVC), pregnancy and children]. Specific recommendations, requirements and/or dedicated studies may be needed depending on the claimed indication (e.g.: acute treatment, long-term treatment, extended treatment) and target population (e.g.: general population with VTE, cancer patients, pregnancy, children, etc.). These aspects are to be discussed for inclusion in the *EMA Guideline on clinical investigation of medicinal products for the treatment of venous thromboembolic disease [CPMP/EWP/563/98]*. The revised guideline will not deal with the development of medicinal products for patients with haemodynamically unstable PE, considered to be candidates for thrombolysis or pulmonary embolectomy.

Some new radiologic techniques, like computed tomography venography (CTV) or magnetic resonance venography (MRV) have been used in several studies during last years and could complement current established techniques in the diagnosis of DVT. CTV has similar sensitivity/specificity to ultrasound in the diagnosis of DVT and also offers assessment of the pelvic and deep femoral veins [Goodman et al, 2007]. CTV leads to the detection of an additional 3% of cases of VTE when combined with pulmonary CT angiography in the assessment of PE [Krishan et al, 2011]. MRV can be highly accurate, easy to perform and successful in many situations where other imaging techniques yield ambiguous results [Glockner & Lee, 2010].

The choice of the comparator may differ depending on the claimed indication (e.g.: LMWH or fondaparinux in acute treatment of VTE; fondaparinux in the treatment of SVT; VKA in the long-term treatment of VTE; LMWH in the acute and long-term treatment of VTE in patients with cancer; placebo in extended treatment, provided that there is no robust evidence for anticoagulation in the target population and therefore the use of placebo is ethical).

Recently, the *EMA Guideline on clinical investigation of medicinal products for prevention of venous thromboembolism (VTE) in patients undergoing high VTE-risk surgery [EMA/CHMP/325170/2012]* and *EMA 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]* 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. In this regard, the assessment of bleeding and hepatic events in the treatment of VTE is at least as important as in prophylaxis trials, because patients may receive higher doses of the antithrombotic drug and for longer periods. In addition, the risk of subsequent arterial thromboembolism is substantially increased in patients who develop VTE [Sørensen et al, 2007]. Therefore, the harmonisation regarding these aspects has to be extended to the revised guideline for treatment of VTE [CPMP/EWP/563/98].

3. Discussion

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

1. Distinction between acute treatment, long-term treatment and extended treatment of VTE (DVT and/or PE), and between treatment of DVT and SVT.
2. Discussion on the need for specific studies in each of the situations mentioned above and in certain special populations (e.g.: VTE associated to cancer, CVC, pregnancy and children).
3. Current place of alternative methods (CTV, MRV) for diagnosis of acute or recurrent DVT and PE in dose-finding and confirmatory trials in comparison with standard diagnostic methods (ascending venography, Doppler US, pulmonary angiography, ventilation/perfusion lung scanning, autopsy in fatal cases).
4. Update of suitable control drugs that may be used in comparative trials.
5. 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.
6. Inclusion of additional secondary safety outcomes of clinical importance for new antithrombotics, like hepatic events or arterial thromboembolism.

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 [CVS WP]/CHMP recommends revising the *EMA Guideline on clinical investigation of medicinal products for the treatment of venous thromboembolic disease* [CPMP/EWP/563/98]. The revised guideline will include an update of several methodological issues related to the treatment of VTE, as described in previous section.

5. Proposed timetable

It is anticipated that a draft Guideline could be agreed by the CVSWP in 4Q2013. The draft may be adopted by the CHMP for release for consultation in 1Q2014. The draft document will then be released for 6 months of external consultation and following the receipt of comments it could be finalised within approximately 3 months.

6. Resource requirements for preparation

The drafting process will be done internally by the CVSWP. 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 drugs for the treatment of VTE. 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 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), clinical trialists in VTE and other Regulatory Agencies.

9. References

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