European Medicines Agency
*Pre-authorisation Evaluation of Medicines for Human Use*

London, 17 November 2005
Doc. Ref. EMEA/CHMP/340660/2005

**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)**

# RECOMMENDATION ON THE NEED FOR REVISION OF THE GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR PROPHYLAXIS OF INTRA- AND POSTOPERATIVE VENOUS THROMBOEMBOLIC RISK (CPMP/EWP/707/98)

| | |
|---|---|
| **AGREED BY THE EFFICACY WORKING PARTY** | 27 September 2005 |
| **ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION** | 17 November 2005 |
| **END OF CONSULTATION (DEADLINE FOR COMMENTS)** | 28 February 2006 |

The proposed guideline will replace the Guideline on Clinical investigation of Medicinal Product for Prophylaxis of Intra- and Postoperative Venous Thromboembolic Risk (EMEA/CPMP/EWP/707/98)

Comments should be provided to Line.Jensen@emea.eu.int

Fax: +44 20 7418 86 13

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 60
E-mail: mail@emea.eu.int http://www.emea.eu.int

INTRODUCTION

A vast number of recent evidence-based randomised clinical trials provide irrefutable evidence that primary thrombo-prophylaxis reduces DVT, PE and fatal PE related to surgery. New international recommendations on intra- and postoperative VTE risk prophylaxis have been issued recently, with new ways of managing DVT in this setting.

A recent risk factor stratification to four (low risk, moderate risk, high risk, highest risk) or to three levels (low, moderate and high risk) allows for the group-specific prophylaxis routinely for all patients who belong to each of the major target groups. Patient-related risk factors are also taken into account in this stratification. The previous EMEA Points to Consider has been adopted 5 years ago, the first discussion took place in April 1998. Since then, new aspects related to the risk identification, the clinical importance of different types of events and the management of patients have evolved. Therefore, it seems necessary to review the guideline.

## 1. PROBLEM STATEMENT

There are several relevant topics for discussion concerning intra- and post-operative VTE prophylaxis:

- Risk factor definition (stratification) and management
- DVT screening methods
- Appropriate endpoints in confirmatory clinical trials
- Duration of treatment/trial
- Populations of special clinical interest
- Safety

## 2. DISCUSSION (ON THE PROBLEM STATEMENT)

1. **Risk factor definition (stratification) and management:** the current guideline mentions “high-risk” and “moderate risk” surgery. A recent risk factor stratification to four (low risk, moderate risk, high risk, highest risk) or to three levels (low, moderate and high risk) allows for the group-specific prophylaxis routinely for all patients who belong to each of the major target groups, the optimisation of prophylaxis and an appropriate management at each risk level. The possibility or not to extrapolate efficacy shown in patients with one risk level to the patients with different risk levels should be discussed. In addition, the possibility to extrapolate the results from one trial done in a high risk patient group (e.g. orthopaedic surgery) to another high risk patient group (of the same risk level) (e.g. abdominal cancer) should also be discussed in the revised guideline.

The choice of comparator(s) will depend on the target population and the corresponding risk level, from no prophylaxis or placebo (for low risk surgery) to e.g. low molecular weight heparins, fondaparinux or oral vitamin K antagonists. The frequency of clinical events is very low on prophylaxis, even in patients with high (or highest) VTE risk. The discussion on trial design should take this into consideration.

2. **DVT screening methods** (ultrasonography versus venography). Contrast venography has long been the diagnostic standard in thromboprophylaxis trials because of its high sensitivity for detecting DVT, notably small or distal thrombi, and the availability of hard copy for blinded assessment. However, the recent guidelines have questioned the clinical relevance of distal DVT. In addition, non-diagnostic rates are of at least 20-40% and inter-observer variability approaches 50%. Moreover, venography is invasive (patients at risk are excluded), not readily repeatable and gives information at a single point of time. This might lead to the inclusion of a population different from patients to be treated in clinical practice.

Venous Doppler ultrasonography is an accepted test for the diagnosis of proximal asymptomatic DVT; it is highly accurate for symptomatic DVT, non invasive and easily repeatable. The recording of the procedure is possible, allowing a centralized analysis of the data. The low sensitivity to detect small and distal DVT may not be a concern if these thrombi are considered of doubtful clinical significance.


 

However, the standardisation of this technique is critical in reducing the potential for the false positive results reported in some trials.

Therefore, the role of each technique and its place in new drug development should be clearly delineated in the revised guideline.

3. **Appropriate endpoints in confirmatory clinical trials** : The asymptomatic distal DVT (diagnosed by venography) is still part of a composite primary endpoint recommended in the current guideline. In addition, the current guideline recommends different primary endpoint for superiority and for non-inferiority trials. This is unusual. More frequently, the same and the most relevant endpoint is chosen as primary endpoint whatever the trial design. However, proving a reduction in all-cause mortality or fatal PE is a problematic task for a thrombo-prophylactic agent as it requires many thousands of patients. A clinically important VTE outcome, such as proximal DVT and PE, were suggested as appropriate endpoints in confirmatory clinical trials in the recently published guidelines on thrombo-prophylaxis. However, the feasibility of such a trial should be discussed due to a very low number of events. In addition, the place of distal (both clinically symptomatic and asymptomatic) DVT in the efficacy assessment should be clearly specified.

The interest of a combined efficacy – safety endpoint (DVT and major bleedings) may also be discussed.

4. **Duration of treatment/trial**: currently, 10-day trial duration is generally recommended. This can not be applied any more; the duration of treatment will depend not only on the indication (e.g. hip fracture: 4-5 weeks, total knee replacement: 10 days) but also on the risks related to patient (e.g. simple abdominal surgery: 10 days, abdominal surgery due to cancer: 5 weeks). This should be further specified in the revised guideline.

5**. Populations of special clinical interest** should deserve more attention in the revised guideline (e.g. very elderly, obese patients, small weights, renal insufficiency, high bleeding risk patients, differences related to gender). A need for stratification on different subgroups should be further elaborated.

In particular, renal insufficiency, very frequent and related to patients' age and surgery itself, increases both VTE risk and bleeding risk. These patients are currently under-represented in clinical trials.

6. **Safety:** the current criteria for major bleeding often underestimate the risk of clinically important bleeding. The definition of major bleeding should be revisited. Calculated blood loss may also be considered. Type of anaesthesia may also be taken into account.

In addition, mechanical methods of prophylaxis may be briefly discussed in the revised guideline; these methods increase venous outflow and reduce stasis and are considered in patients with high bleeding risk, or when used in combination with anticoagulant prophylaxis to improve efficacy.

## 3. RECOMMENDATION

The Efficacy Working Party/CHMP recommends to draft/ revise a Guideline on Clinical Investigation of Medicinal Products for Prophylaxis of Intra- and Postoperative Venous Thromboembolic Risk (EMEA/CHMP/EWP/707/98).

The revised guideline will address the risk factor definition (stratification) and management, the utility of different DVT screening methods (venography versus venous Doppler ultrasonography), relevant endpoints in confirmatory clinical trials and the feasibility of trials in different risk groups, duration of treatment/trial, populations of special clinical interest and safety concerns.

## 4. PROPOSED TIMETABLE

*Release for consultation on November 2005*

*Deadline for comments February 2006*

*Discussion in EWP April 2006*

*Discussion with PhvWP May 2006*

*Proposed date for release of draft guideline June 2006*

 

*Deadline for comments December2006*

*Re-discussion in EWP January 2007*

*Expected dated for adoption by Committee February 2007*

## 5. RESOURCE REQUIREMENTS FOR PREPARATION

A Rapporteur and a Co-Rapporteur have been appointed to work on the revision of this Guideline. The topic will be on the EWP agenda for discussion for an estimated 3 meetings. Further discussion is planned to take place in 1 pharmacovigilance working party meeting next year.

## 6. IMPACT ASSESSMENT (ANTICIPATED)

Since the adoption of the previous CHMP guidance in this field, a larger body of scientific evidence has become available from a number of clinical studies showing that primary thrombo-prophylaxis reduces DVT, PE and fatal PE related to surgery. Changes in the way patients are managed, risk identification, and clinical importance of different types of events need to be incorporated in the guideline.

It is anticipated that the availability of up-to-date guidance would facilitate the design of clinical trials and their assessment and could thereby translate into a beneficial impact on public health, through a better level of prevention of thrombo-embolism events related to surgery.

## 7. INTERESTED PARTIES

- International Surgical Thrombosis Forum (ISTF)
- Association of Clinical Research Organizations (ACRO)
- European Federation of Immunological Societies (EFIS)
- European Society for Cardiology
- Société Française D'anesthesie et de Reanimation (SFAR)

## 8. REFERENCES TO LITERATURE, GUIDELINES ETC

1. Geerts W, Pineo GF, Heit JA et al. Seventh ACCP Consensus Conference on Antithrombotic Therapy. Prevention of venous thromboembolism. Chest 2004;126:338S-400S

2. Société Française d'Anesthésie et de Réanimation. Prevention de la maladie thromboembolique veineuse périopératoire et obstetricale. Recommandations pour la pratique clinique. Texte court 2005.

 