The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

London, 16 December 1999
CPMP/EWP/563/98

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

NOTE FOR GUIDANCE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR THE TREATMENT OF VENOUS THROMBOEMBOLIC DISEASE

DISCUSSION IN THE EFFICACY WORKING PARTY (EWP)	April 1998 – January 1999
TRANSMISSION TO THE CPMP	February 1999
RELEASE FOR CONSULTATION	February 1999
DEADLINE FOR COMMENTS	August 1999
RE-DISCUSSION AT THE EWP	September 1999 – November 1999
ADOPTION BY THE CPMP	December 1999
DATE FOR COMING INTO OPERATION	June 2000

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CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR THE TREATMENT OF VENOUS THROMBOEMBOLIC DISEASE

PREAMBLE

These notes describe the type of clinical development programme that should support the registration of new medicinal products for the indication treatment of venous thromboembolism (VTE). The development programme recommended for the indication prevention of VTE is addressed in a separate document.

These notes are intended to assist applicants during the development phase and are for guidance only. Any deviation from guidelines should be explained and discussed in the Expert reports. They should be read in conjunction with Directive 75/318, as amended, and other pertinent elements outline in current and future EU and ICH guidelines especially those on:

- Studies in Support of Special Populations: Geriatrics (ICH topic E7)
- Dose Response Information to Support Drug Registration (ICH topic E4)
- Statistical Principles for Clinical Trials (ICH topic E9).

1. INTRODUCTION

Venous thromboembolism (VTE) may present clinically as deep vein thrombosis (DVT), pulmonary embolism (PE) or both. The reported annual incidence of VTE in Western countries is estimated to be approximately 1-2/1,000. A transient or permanent risk factor for VTE is demonstrable in a large fraction of patients.

There is good evidence that DVT and PE may be considered as expressions of one and the same disease:

- In different studies, patients presenting with venographically proven DVT have been shown to have evidence of silent PE in 30-50% of cases.
- Patients with proven PE will have DVT in 50-70% of cases.

Since the basic treatment strategy for patients with DVT and PE is also similar, it is considered relevant that efficacy and safety studies of new treatment modalities in this area should include patients with DVT and/or PE, *i.e.* VTE.

The choice of treatment in VTE should be based on the clinical impact of the disease, which ranges over a spectrum from patients with large thrombotic masses and extensive symptomatology, who may need aggressive therapy, to patients with minimal, distal, thrombosis with no tendency for recurrence, who might be safely managed by a watchful "wait and see" strategy involving repeated non-invasive investigations, with treatment reserved for those with extending disease. The majority of patients, however, will have moderate to severe VTE, and the documentation of medicinal products for this category forms the thrust of this document. This guideline does not deal with the development of medicinal products for patients with massive PE, considered to be candidates for thrombolytic therapy or surgical embolectomy.

Currently accepted initial management of VTE consists of at least 5 days of intravenous (i.v.) or subcutaneous (s.c.) unfractionated heparin (UH), or s.c. low-molecular-mass heparin (LMMH). Therapy aims are to prevent extension of the thrombus, (fatal) pulmonary embolisation and early recurrence.

Several well-designed trials have shown that follow-up oral anticoagulant therapy with vitamin K antagonists reduces the risk of recurrent VTE for the duration of therapy. Whether the benefit of such treatment also extends to the incidence of the third main sequel of VTE, the post-thrombotic syndrome, has not been documented. There is very good evidence that the duration of therapy should be adapted to the risk for VTE recurrence in the patient population under study and that patients with chronic risk factors for recurrence may be candidates for life-long anticoagulant prophylaxis.

2. PATIENTS TO BE STUDIED

It is expected that clinical trials will focus on patients with symptomatic, usually proximal (extending above knee level), DVT and/or symptomatic PE. If patients with purely distal (below-knee) DVT are included, a stratification into proximal or distal DVT at inclusion is recommended. Efficacy and safety data gained in patients with proximal DVT should, otherwise, be useful for patients with extending distal DVT, in definite need of anticoagulant therapy. Stratification of the study population regarding the presence of symptomatic PE at baseline should also be undertaken. If the claim treatment of PE is intended, sufficient representation of patients with PE should be ensured. However, patients with PE could also be studied separately.

The population encountered in clinical practice will be heterogeneous with regard to the presence of identifiable risk factors for VTE and comorbidity. This has major impact on the risk for recurrences during and after therapy, as well as all-cause mortality. To increase assay sensitivity, only patients with reasonable remaining life expectancy should be included. It is also important that studied patients are well characterised and that treatment groups are comparable regarding risk for recurrent VTE. Factors that should be taken into consideration include:

- Recent surgery or trauma
- Immobilisation
- Previous episodes of VTE
- Pregnancy or oestrogen use
- Neoplastic disease

Prothrombotic states (*e.g.* deficiencies of AT III, resistance to activated protein C, lupus anticoagulant, antiphospholipid antibody, hyperhomocysteinemia, mutations to the prothrombin gene, etc).

3. DIAGNOSIS OF VTE

More than half of patients presenting with clinical signs and symptoms suggestive of DVT and/or PE will not have objective proof of these disorders. The following diagnostic methods are considered acceptable for documentation of DVT and PE in studies of drug efficacy and safety:

3.1 DVT

- Ascending venography is presently regarded as the standard method. For this method a quantitative system has been reasonably validated and it allows (blinded) centralised reading or reading by several observers. The method may be of low acceptability to the patient, especially for repeated examinations.
- Compression ultrasonography (US) examination has been documented to have adequate sensitivity and specificity in symptomatic, proximal DVT, but is less adequate for distal

DVT. The findings can be interpreted by the observer only, who should be well trained and carefully selected by the study co-ordinator.

Recurrent DVT during or after therapy may be demonstrated through:

- The finding of a new or extended intraluminal filling defect seen on at least two projections during repeat ascending venography.
- The finding of abnormal results on US examination indicating thrombosis in a previously normal area in the case of proximal DVT.
- Diagnosis of recurrent DVT based solely on clinical signs and symptoms is discouraged. The number of such episodes, especially if leading to changed or renewed therapy, must, however, be noted and accommodated for in the analyses (see section 4.2).

3.2 PE

- Pulmonary angiography is the gold standard.
- Spiral computed tomography (for large segmental emboli).
- Ventilation-perfusion (V/Q) lung scanning is the method that has been most frequently used for the diagnosis of PE in clinical trials so far. A normal V/Q scan or perfusion scan is considered adequate to rule out clinically important PE. Only so-called "high probability" findings on V/Q scan are specific enough to allow a positive diagnosis of PE. Other types of findings should be regarded as "non-diagnostic" and should be verified through pulmonary angiography.
- In the presence of symptoms indicative of PE in a patient with demonstrated DVT, "non-diagnostic" findings on V/Q scan are sufficient for a diagnosis of PE.

Recurrent PE during or after therapy may be demonstrated through:

- Repeat pulmonary angiography with the finding of a new intraluminal filling defect or a new, sudden cut-off in an arterial branch, not present on the first examination.
- Repeat spiral computed tomography showing new embolism
- Repeat V/Q scan with the finding of a new perfusion defect, segmental or larger, with a ventilation mismatch.
- Demonstration of fresh PE at autopsy.

4. EFFICACY AND SAFETY ENDPOINTS

All endpoints must be defined prior to the start of the trial and included in the study protocol.

4.1 Exploratory trials

Dose-ranging studies should aim to establish as robust as possible dose-response information in relation to clinically useful methods for monitoring of anticoagulant effect. Pharmacodynamic data obtained in preclinical studies should be taken into account.

For proof-of-concept and dose-ranging studies aiming to document the effects of initial treatment on thrombus extension and/or recurrence, repeat examinations should be undertaken after 5-10 days. Bilateral ascending venography with quantitative scoring is the standard method. Repeat US examination is an acceptable alternative. Baseline and end-of-treatment V/Q lung scanning should also be performed. A combined endpoint based on findings from venography/US examination and V/Q scan may be useful.

For medicinal products intended for follow-up therapy after initial treatment of DVT/PE, no data on clinical or surrogate clinical efficacy endpoints are expected from Phase II trials

The safety evaluation should focus on the incidence of bleeding. Bleeding should be classified as major or minor. The following criteria for major bleeding can be used:

- fatal bleeding
- clinically overt bleeding causing a fall in Hb level of 20 g/l or more, or leading to transfusion of two or more units of whole blood or red cells
- bleeding in areas of special concern, such as retroperitoneal, intracranial, intraspinal or intraocular bleeding
- bleeding causing permanent treatment cessation

All other bleeds will be classified as minor bleeds.

4.2 Confirmatory trials

Phase III trials should primarily address clinical outcome in the form of:

- Recurrent, symptomatic VTE (nonfatal DVT and/or nonfatal PE)
- Deaths
- Bleeding episodes

All major endpoints should be adjudicated by a blinded clinical events committee.

Recurrent DVT and PE should be objectively verified (see section 3). If, in exceptional cases, recurrent events diagnosed only by clinical symptoms are followed by acute, new antithrombotic therapy, such events could be considered for inclusion in the endpoint only after adjudication by the clinical events committee. Sensitivity analyses should be performed to explore the robustness of the conclusions of the study to the decisions of the clinical events committee regarding cases of unconfirmed VTE.

Deaths should be carefully characterised regarding their relationship to VTE, according to criteria specified in the study protocol.

The primary efficacy endpoint should be a composite of recurrent, symptomatic, nonfatal DVT/PE and mortality.

Two analyses should be performed:

1. The combined incidence of recurrent DVT/PE and all deaths. This analysis will be considered most important in trials aiming to show superiority of the medicinal product under consideration.
2. The combined incidence of recurrent DVT/PE and deaths related to VTE. This analysis will be considered most important in trials aiming to document non-inferiority. In this situation special care should be taken to include patients with reasonable remaining life expectancy.

Secondary analyses should include separate analyses of the components of the primary endpoint.

Subgroup analyses are encouraged, to illustrate outcome in relation to level of extension of DVT, to the presence or absence of a history of previous episodes of VTE, and to severity of PE, *e.g.* as indicated by clinical or echocardiographic evidence of right ventricular failure.

The incidence of bleeding is the major safety variable. Bleeding episodes should be classified as outlined above (section 4.1). In the overall safety evaluation, adequate attention should also be given to the incidence of idiosynchratic episodes and other, rare, unexpected effects.

In studies evaluating medicinal products intended for the initial treatment phase of VTE, the study period for primary evaluation should be at least three months. To increase the difference-detecting ability of these studies, a further evaluation of clinical outcome is recommended at the time of cessation of the initial phase of therapy in the control arm, or no later than on day 8-10.

In trials of medicinal products intended for follow-up anticoagulant therapy the timepoint for primary evaluation must be related to the presence of non-transient risk factors for recurrent VTE in the population under study. Unless otherwise justified, controlled data on a sufficient number of patients at high risk for recurrent VTE (thrombophilia or idiopathic proximal DVT), treated for at least six months should be presented. For medicinal products intended for chronic use, safety data extending beyond this period should also be presented.

5 STUDY DESIGN

5.1 Human Pharmacology

5.1.1 Pharmacodynamics

The initial studies should determine the general safety of the compound and should provide an indication of doses of potential clinical relevance and of their effects on clinically useful monitoring variables for anticoagulant effect.

5.1.2 Pharmacokinetics

The pharmacokinetic information required is stated in detail in the guideline on ”Pharmacokinetic Studies in Man”.

5.1.3 Interactions

Systematic pharmacokinetic and pharmacodynamic interaction studies should be performed if results of clinical trials or the pharmacokinetic and pharmacodynamic properties of the drug give reason to suspect interaction problems. Further advice is given in the Guideline on ”Interactions”. Special attention should be devoted to the potential of unwanted interactions with drugs likely to be administered concomitantly in the target population, such as non-steroidal anti-inflammatory agents, diuretics, digitalis glycosides and antihypertensive agents

5.2 Dose Response Studies

These studies should usually be performed against a justified comparator drug (see section 5.3.3) and should be designed to provide dose-response information regarding accepted intermediate endpoints (see section 4.1).

5.3 Main Therapeutic Studies

5.3.1 General Comments

Clinical studies in this therapeutic area will be comparator-controlled. As usual, this requires extra precaution in planning and conducting the studies. Sample size calculations as well as decisions regarding study design (superiority vs. equivalence/non-inferiority) must take into account expected event rates with current therapeutic strategies in the population under consideration. Criteria for equivalence/non-inferiority must be predefined and well discussed regarding their clinical relevance. Further advice is given in the ICH E9 (“Statistical Principles for Clinical Trials”) and ICH E10 (“Choice of Control Group in Clinical Trials”) guidelines.

Sample sizes should be sufficient to allow conclusions regarding benefit/risk in different groups according to stratification and should also take into account the desirability of subgroup analyses regarding factors mentioned above, as well as age, gender and body weight.

5.3.2 Blinding

It is acknowledged that double-blind trials are difficult to perform, at least in the initial treatment of VTE. If blinding is not considered possible, adjudication of endpoint events by an independent committee, blinded to the treatment of the patient, is especially important. For follow-up oral therapy, double-blind trials should be possible, and investigators in this stage should be blinded also to the treatment given to the patient during the initial treatment phase.

The potential for bias should further be minimised through measures such as enrolment of consecutive patients, central randomisation and complete follow-up of all patients.

5.3.3 Comparator drugs

UH, given as a continuous i.v. infusion for at least 4-7 days and dose-titrated to an aPTT value 1.5-2.5 times the control value is an accepted comparator for the evaluation of new medicinal products for the initial phase of anticoagulant treatment of DVT and PE. The performance characteristics and reproducibility of the aPTT method used should be well documented. Plasma heparin levels could be used to further illustrate heparin exposure. An LMMH is an accepted comparator for the evaluation of new medicinal products for the initial phase of anticoagulant treatment of DVT. If an LMMH is used as comparator in studies in PE, this should be justified by relevant literature data.

For the phase of follow-up therapy, an oral vitamin K antagonist, dose-titrated to an International Normalised Ratio (INR) of 2.0-3.0, is the accepted comparator drug. The level of anticoagulation achieved must be well documented for the entire treatment period.

5.3.4 Study population and duration

The recommended population for study is described in section 2.

Recommendations regarding study duration are given in section 4.2.