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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

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EXECUTIVE SUMMARY

This guideline is intended to provide guidance for the evaluation of new medicinal products in the primary prophylaxis of venous thrombo-embolic risk in the non-surgical setting. This guideline should be read in conjunction with Directive 2001/83/EC and all other pertinent elements outlined in current and future EU and ICH guidelines and regulations, especially those on:

Dose-Response Information to Support Drug Registration (ICH E4),

Statistical Principles for Clinical Trials (ICH E9),

Choice of Control Group in Clinical Trials (ICH E10),

The Extent of Population Exposure to Assess Clinical Safety for Drugs (ICH E1A),

Prophylaxis of intra- and post-operative venous thromboembolic risk CPMP/EWP/707/98

One pivotal study CPMP/EWP/2330/99

Investigation of drug interactions CPMP/EWP/560/95

This document is only for guidance but any deviation should be explained and discussed in the Expert reports/ Clinical Overview.

1. INTRODUCTION (BACKGROUND)

The majority of patients developing VTE are non-surgical, accounting for 3 out of 4 fatal pulmonary emboli. There is currently an approved 'CPMP Point to consider document on clinical investigation of medicinal products for prophylaxis of intra- and post-operative venous thromboembolic risk' (CPMP/EWP/707/98). However, this was not intended to address the issue of prophylaxis in non-surgical indications. The predisposing risk factors might differ between surgical and non-surgical patients.

The scope of this document does not include the prevention of long-term sequelae such as post-phlebitic syndrome.

Venous thromboembolic disease (VTE) is a common condition, with clinically recognised deep vein thrombosis (DVT) and/or Pulmonary Embolism (PE) and with a reported annual incidence of 2 per 1000 general population. As clinical diagnosis of VTE is unreliable with poor sensitivity and specificity and as the condition is often asymptomatic, prophylaxis is currently considered to decrease morbidity and mortality related to VTE in high-risk situations.

The primary aim of prophylaxis and/or treatment in the setting of thrombo-embolism, in clinical practice, is the prevention of PE, both fatal and non-fatal, usually resulting from proximal DVT of the lower limb venous system. Distal DVTs are considered less serious unless propagating proximally.

Several factors predispose to the development of VTE as detailed below.

2. PATIENTS CHARACTERISTICS AND SELECTION OF PATIENTS

Predisposing Factors

There are a number of factors that are considered important predisposing risk factors for VTE. These include,

- Demographic factors such as obesity and advanced age
- Prolonged immobilisation due to whatever cause
- Prior history of DVT/PE, hypercoagulable states such as deficiency of anti-thrombin[1], protein C and protein S

- Existing clinical disease states such as stroke, cardiac disease including recent myocardial infarction, respiratory insufficiency, malignant disease, inflammatory bowel disease, varicose veins, trauma, polycythaemia, paraproteinaemia
- Iatrogenic causes such as oral contraceptive use and Hormone Replacement Therapy (HRT).

The strength of association for each of the factors is variable. It is important that the trial population is reflective of the variety of predisposing risk factors.

Patient care and other factors

In addition to the predisposing factors inherent in the clinical status and demography of the patient population to be studied, the risk of development of VTE and efficacy/ safety of the test product in development can be further confounded by a variety of factors such as investigator and site specific standards of care and concomitant illness and/or treatment.

- Practice of early mobilisation and physiotherapy; use of mechanical prophylaxis measures (elastic compression stockings, intermittent pneumatic compression)
- Use of drugs which could interfere with platelet function such as aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs)
- Diseases which could impair coagulation such as liver disease
- Potential interaction by drugs used to treat underlying diseases such as cancer; poly-pharmacy in case of elderly patients with multiple pathology
- Poly-pharmacy in case of elderly patients with multiple pathology

The potential for any of these to affect the efficacy and safety (through effects on pharmacodynamics and/or pharmacokinetics) of the product under evaluation should be prospectively identified.

Patient Selection

Patients should be selected on the basis of target population and intended indication. If a 'general indication' is intended, it is important that the trial population has adequate representation of several applicable subgroups e.g., stroke, cardiac disease, cancer and infection/ inflammation, due to the heterogeneous nature of predisposing factors. If the main therapeutic study were conducted in a single group of patients e.g., cardiac disease, the indication would be restricted to that group of patients only. In addition to immobilisation there should be preferably at least one additional risk factor present in the patients in clinical trials.

It is unlikely that results from studies of patients with acute illnesses will be applicable as pivotal evidence to those with chronic diseases and vice-versa, but can be used as supporting evidence. However, exploratory trials might be applicable to all clinical situations (see Dose selection and Duration of treatment)

3. METHOD TO ASSESS EFFICACY

Efficacy assessment should take into consideration the intended target population and the duration of treatment, taking into account that benefits may be seen for a variable period after completion of treatment.

Since the main objective will be to prevent symptomatic/fatal PE, evaluation of efficacy will need to focus on confirmation of diagnosis of proximal DVT and non-fatal/fatal PEs and document the clinical impact on morbidity/ mortality.

Diagnosis of PE could be based on any of the established tests such as ventilation / perfusion scans, pulmonary angiography, spiral CT or MRI. Clinical features such as cyanosis, dyspnoea, tachycardia and hypotension should be documented to enable assessment of severity but are not sufficient for diagnosis because of lack of specificity and low sensitivity. Similarly changes in electro-cardiographs, pulse oximetry and chest x-ray cannot be relied upon for diagnosis but may be used as auxiliary tests.

Since sudden death may be the first sign of PE and is the most important complication of it. Lack of confirmation or elimination of PE as the cause of death can have important implications for efficacy assessment. In cases of 'suspected fatal PE,' effort should be made to obtain an autopsy to confirm the diagnosis. Unless PE has been excluded, it will be difficult to attribute any death to non-PE causes.

DVT may be diagnosed by bilateral ascending venography or ultrasound assessment. If using ultrasound, a method with high sensitivity and specificity should be chosen.

Whichever diagnostic method is chosen, the same method should be used for the entire study to provide consistency.

Since heparins are known to affect D-Dimer results, such results may not be useful in excluding thrombosis in prophylaxis trials.

Dose selection and duration of treatment

Appropriate dose response studies should be carried out, unless relevant information is already available.

In certain cases, where there is strong and confirmed evidence, a laboratory test could support dose-selection; the assay used should be a validated test and should preferably be the same for all participating patients. Such assay results would typically be applicable for efficacy monitoring, although it would be advantageous to have applicability for safety purposes also.

The duration of treatment intended for each clinical indication should be adequately reflected in the studies and the duration chosen should be justified. In the case of surgical patients, the duration is usually 10 days.

- In the case of acute medical illness, when patients have reduced mobility or are immobilised, treatment should be administered until full mobilisation prior to discharge. The duration of treatment in this situation is usually for 7-14 days.
- In the case of sub-acute illness, where the condition is reversible, but prophylaxis is needed out of hospital, due to reduced mobility, treatment should be continued until full mobilisation. The duration of additional treatment in this situation is likely to be for 2-4 weeks after discharge.
- If the indication proposed is for a chronic irreversible condition(s), such as established paralysis due to cerebrovascular disease, where the treatment may be given long-term or indefinitely, the trial duration should be of reasonable length – at least 3-6 months – to be able to provide sufficient reassurance of efficacy and at least 6-12 months for safety.

The level of benefit that is demonstrated should be clinically relevant for each clinical situation.

Control groups

Standard of care or placebo control will usually suffice for superiority trials. If an active treatment exists this should be included in the study design, otherwise it should be fully justified.

Primary Efficacy Endpoints

In therapeutic confirmatory studies designed to show superiority of a new agent over placebo, the primary endpoint should be a composite endpoint consisting of the following events:

(i) well documented proximal DVT

(ii) well documented non fatal PE idem

(iii) Death from all causes including PE (see section on Therapeutic confirmatory studies).

In therapeutic confirmatory studies designed to show the non-inferiority of a new agent to an existing agent, the primary endpoint should be a composite end point consisting of the following events:

(i) well documented proximal DVT

(ii) Symptomatic and well documented non fatal PE

(iii) VTE related deaths.

The difference in endpoints between superiority and non-inferiority trials is based on the need for a more sensitive endpoint in the latter.
In both cases, a supportive analysis of the composite endpoint should be provided using the alternative group of deaths i.e. VTE- related deaths for a superiority trial and all cause deaths for a non-inferiority trial.

Separate analyses of the components should be provided, including proximal and distal DVT when available. Treatment effects on this composite endpoint should be reflected in an effect on both DVTs and/or PEs, showing at least positive trends when recorded. There should be no adverse effects on PE and mortality (See Secondary Efficacy Endpoints).

In order to prevent bias, it is highly recommended that an independent committee of experts who are blinded to the allocation adjudicate the occurrence and classification of all components of the composite endpoint.

All deaths must be reported. Deaths should be carefully characterised regarding their relationship to VTE. Criteria for classifying deaths according to cause should be provided in the protocol. Special care should be taken to include patients with reasonable life expectancy in clinical trials.

At an initial stage of the development (see section III.1 Early studies in humans) the incidence of patients with DVTs, which may or may not be symptomatic, within a certain period of observation, may be an appropriate endpoint.

Secondary Efficacy Endpoints

These endpoints will be assessed to check the consistency of the conclusion drawn on the basis of the results of the primary endpoints. The following secondary endpoints need to be considered:

- Incidence of all DVTs. Proximal and distal DVTs should be analysed separately.
- Incidence of symptomatic DVTs
- Incidence of documented symptomatic venous thromboembolic events (PE and / or DVTs) within a follow-up period after trial drug discontinuation, usually 4 to 6 weeks, standardised as completely as possible, and treated in a comparable way in all treatment arms of the trial.
- Death from PE
- Death from all causes

4. STRATEGY AND DESIGN OF CLINICAL TRIALS

Main features of clinical trial designs

Pivotal trials should be double blind, randomised and controlled. Even if blinding is not possible the trial should be controlled and randomised. In such trials, evaluation of efficacy and safety should be carried out by independent adjudication committees.

4.1 Early Studies in Humans

A dose-response evaluation should be carried out to justify the intended clinical dose (see under Dose Selection above).

The use of a placebo-control group when ethical is strongly recommended during dose finding studies. Similarly, the use of an active control group is encouraged in order to ‘calibrate’ the efficacy and safety observations made on the compound under development.

The primary endpoint at this stage could be the incidence of DVTs during the treatment period providing proof-of-concept.

4.2 Therapeutic Confirmatory Studies

The aim of phase III clinical development is:

- To prove that the risk benefit of the medicinal product of interest is comparable to an established comparator for prophylaxis of VTE in the target population.
- In situations when no prophylactic methods have yet been registered in the targeted indication superiority over placebo should be demonstrated for the medicinal product combined with an acceptable safety profile.

The therapeutic indication should reflect the results of the clinical trials. Depending on the intended indication, the relevant cross-section of the patient population should be represented in the trials. An extrapolation to other clinical situations that were not represented in the trials and/or a separate indication based on a sub-group analysis is not desirable.

All non-drug treatment measures should be standardised.

4.3 Studies in special population

This should be assessed as dictated by the product and the target indication.

In general, the following groups may be vulnerable to adverse effects of drugs and might require specific evaluation.

- elderly (>70 years)
- extremes of body weight
- renal failure
- liver disease

It is desirable to have the elderly and those with extremes of body weight represented in the main therapeutic confirmatory trials. As long as there is a reasonable representation of the above sub-groups of patients in the main therapeutic study, a separate study is not considered necessary.

Safety should be prospectively assessed for inclusion of the sub-groups in SPC. If monitoring is required, it is recommended that this be assessed in the main trials.

Drug Interactions

Many of the patients are likely to be on other medications, either established or current, with a potential for drug interaction. This may have consequences for safety and / or efficacy.

For pharmacokinetic interactions relevant guidelines and product particulars should be consulted.

The possibility of a pharmacodynamic interaction, considered important for drugs used in this indication, should also be evaluated. It is not possible to list all the potential interacting drugs in this document. Some common examples to be considered are NSAIDs and anti-platelet agents.

5. CLINICAL SAFETY EVALUATION

5.1 Safety evaluation will depend on the product under consideration and its potential for adverse effects, depending on its mode of action and pharmacological class. If an anticoagulant is to be tested, bleeding is the most important safety issue that will need a thorough evaluation.

There should be consistency in the method used for assessing bleeding associated with the medicinal product of interest across the entire development program. A validated and clinically relevant classification of bleeding episodes should be used. Similar to the efficacy evaluation, the adjudication of bleeding events by a central independent and blinded committee of experts, using pre-specified limits and clear terms of reference is strongly encouraged.

Bleeding episodes should be classified as major or minor. Examples of major haemorrhage include:

- Fatal haemorrhage
- Bleeding associated with a fall in haemoglobin level of ≥20g/l
- Haemorrhage requiring resuscitation with transfusion of two or more units of whole blood or packed cells

- Symptomatic haemorrhage in a critical area or organ, such as intracranial, intraspinal, retroperitoneal, pericardial bleeding

The definition of major and minor haemorrhage should be in accordance with the International Society on Thrombosis and Haemostasis (ISTH) Guidelines.

As support for the conclusions drawn from the main safety criteria such as the incidence of patients with major bleeding episodes, other haemorrhage related parameters should be recorded during the studies e.g.:

- Haemoglobin level, haematocrit changes during the treatment period.
- Amount of blood loss, quantified by an objective method.
- Incidence of patients receiving transfusion of whole blood or packed red cells and transfused quantities during the treatment period.

Lastly the mechanism of action and pharmacological class of the medicinal product under investigation may suggest specific aspects of safety evaluation which should be considered for incorporation into the entire development program (e.g. platelet counts, antibody detection, etc.).

For biotechnology derived product(s), immunogenicity should be evaluated prospectively. The type of antibody (e.g. neutralising) and incidence of immune mediated adverse events should be assessed and clearly documented.

5.2 Extent of population exposure to assess clinical safety

As non-surgical patients at-risk of VTE constitute a sizeable population, it is likely that safety evaluation will need to be carried out in several hundred to a few thousand patients, prior to approval. For a chronic, indefinite duration of treatment, the studies should be of at least 6-12 months duration, in accordance with ICH requirements, to be able to provide sufficient reassurance of safety.

5.3 Long term safety

Haemorrhage is the most important risk and should be evaluated in detail. Reference should be made to relevant guidelines (ICH 1A).

6. OTHER INFORMATION

Monitoring in use

Low molecular weight heparins do not generally require routine laboratory monitoring. Whether or not a product requires monitoring should be assessed on a case-by-case basis under proposed conditions of use.

If monitoring is required for efficacy and / or safety reasons, this should be identified and studied prospectively in order for it to be included in SPC. Validated methods, which are available under normal conditions of proposed use of the product, should be assessed.

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[1] CHMP guidance on antithrombin products (Clinical investigation of plasma derived antithrombin products (CPMP/BPWG/2220/99) and core SPC (CPMP/BPWG/3226/99)).