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POINTS TO CONSIDER ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR PROPHYLAXIS OF INTRA- AND POST-OPERATIVE VENOUS THROMBOEMBOLIC RISK

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Points to Consider have been developed to provide advice on selected areas relevant to the development of medicinal products in specific therapeutic fields.

This document will be revised in accordance with the scientific advances made in this area.

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CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR PROPHYLAXIS OF INTRA-AND POST-OPERATIVE VENOUS THROMBOEMBOLIC RISK

PREAMBLE

This document describes the type of clinical development programme that should support registration of a medicinal product for the primary prophylactic management of venous thromboembolic risk in the surgery setting. The non surgical situation, which raises different issues, will not be addressed here.

The scope of this points to consider paper is restricted to the prevention of acute venous thromboembolic events, i.e. Deep Vein Thrombosis (DVT) and/or Pulmonary Embolism (PE), that involve or originate from lower limb veins. It does not discuss the prevention of long term sequelae such as post phlebitic syndrome or venous thrombosis in upper extremities which should be considered as different pathophysiological entities.

1. BACKGROUND INFORMATION

The formation of a thrombus in a deep vein predisposes patient to various complications :

- PE, which may be the initial clinical manifestation of a DVT
- clinical symptoms related to local hemodynamic changes and inflammatory reactions
- and long term sequelae such as the post-phlebitic syndrome.

Some locations of deep vein thrombosis are considered to be at higher risk for complications than are others. For instance DVT of the proximal veins are considered to be the most dangerous, even though distal DVT are more frequent. However there is no consensus as to the clinical impact of some distal DVT, especially for the risk of PE.

The clinical situations with an increased risk for developing acute venous thromboembolism, where prevention should be applied include :

- surgery with “high” risk for developing venous thromboembolism such as major orthopedic surgery of the lower limbs (e.g. elective hip or knee surgery, hip fracture and spine surgery, etc) or cancer surgery (e.g. colorectal surgery) where, in the absence of prevention it has been repeatedly demonstrated that more than 50% of patients would develop angiographic DVT.
- surgery with “moderate” risk for developing venous thromboembolism such as major soft tissue surgery of benign disease.

2. PATIENTS CHARACTERISTICS

2.1 Demographics

In addition to the well documented variations in risk for developing venous thromboembolism that depend on the clinical situation, as described above, a variety of patient characteristics (e.g. age, obesity, varicosae, cancer, congestive heart failure, respiratory insufficiency, prior venous thromboembolism and haematological risk factors, eg factor V leiden, oral contraceptives) may affect this risk and potentially confound the assessment of the medicinal product of interest.

Just as with the risk of development of venous thromboembolism, the risk of bleeding may also vary depending upon the patient population defined (e.g. age, body weight, etc.) and so the

risk/benefit of the medicinal product of interest may vary between classes of patients.

Therefore, clinical development in this field requires evaluation of treatment effect within pre defined, and homogeneous patient groups. A sufficient number of patients with intrinsic risk factors for VTE (i.e other than the surgical procedure), such as the elderly and specifically the very old (patients between 70 and 90 years of age) where appropriate , should be evaluated in clinical trials in order to permit an adequate benefit / risk assessment at the optimal dose of the drug in this population.

2.2 Patient Care Characteristics

In addition to risk variation that is inherent to the clinical situation and demography of interest, the risk of development of venous thrombosis and the safety risk can be confounded by a variety of investigator and site specific standards of care e.g., in orthopedic surgery, type of anaesthesia (particularly spinal anesthesia) cemented or cementless prosthesis, time to ambulation and modalities of physiotherapy, including mechanical prophylactic measures (i.e. elastic graduated pressure stockings, intermittent pneumatic compression devices) and the use of non steroidal anti-inflammatory drugs and other drugs interfering with platelet functions (aspirin, etc.). The potential for any of these concomitant therapeutic modalities to interfere with the safety and efficacy profiles of the medicinal product of interest should be prospectively identified.

In such cases, the clinical studies should be designed to decrease any potential bias due to unbalanced therapeutic modalities between treatment groups .

The concomitant use of these therapeutic management tools, including other drugs, during the clinical development of a medicinal product for the prophylactic management of venous thromboembolic risk needs therefore to be specifically defined as part of or in addition to the definition of the studied population and should be standardised as much as possible in the main therapeutic trials.

Additional potential interactions may need to be assessed in specific studies depending on pharmacokinetic features of the drug under evaluation.

3. ASSESSMENT OF EFFICACY

The choice of the primary efficacy endpoint depends on the targeted labelling of the indication for the drug under development. Whatever this choice, the primary efficacy endpoint that will be considered should have been demonstrated to be clinically relevant.

An important objective will be to demonstrate that the medicinal product decreases the number of patients developing DVT's within the prophylatic treatment period. Proximal DVT's, distal DVT's and their total may all be of interest in therapeutic confirmatory studies, depending upon the objective of the study

A suitable test for the detection and diagnosis of DVT's is bilateral ascending venography. It is mandatory that this test should be performed in every patient at a fixed time point, namely at the end of the prophylactic treatment period. Ultrasonography may also be used for the diagnosis of proximal DVT's provided it is performed by experienced investigators blinded to the treatment group. In case other diagnostic methods are considered, the relevance of such methods - especially their specificity - should be justified by the applicant

3.1 Primary Efficacy Endpoint

In therapeutic confirmatory studies designed to show superiority of a new agent to an existing agent, the primary endpoint should be a composite endpoint consisting of the following events: (i) proximal DVT's or any (proximal plus distal) DVT's (ii) symptomatic and well documented (i.e. perfusion/ventilation lung scan, spiral computer tomogram,and/or pulmonary angiography) non fatal PE (iii) death from all causes including PE (see section 5.2 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) proximal DVT's ii) symptomatic and well documented non fatal PE (iii) VTE related deaths.

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 of the composite should be provided, including proximal and distal DVT's when available.

Treatment effects on this composite endpoint should be reflected in an effect on DVT's alone, showing at least positive trends for both proximal and distal DVT's when recorded. There should be no adverse effects on PE and mortality.

In order to prevent bias, it is highly recommended that the occurrence and classification of all components of the composite endpoint is adjudicated by an independent and blind committee of experts.

All deaths must be reported. Deaths should be carefully characterized regarding their relationship to VTE through adjudication by the blinded clinical events committee. Autopsy should be performed whenever possible. Criteria for classifying deaths according to cause should be provided in the protocol. Special care should be taken to include in clinical trials patients with reasonable life expectancy

At an initial stage of the development (see section 5.1 Therapeutic exploratory studies) other primary efficacy endpoints may be proposed, such as the incidence of patients with venographic proximal and distal DVT's within a certain period of observation.

3.2 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 DVT's. Where total DVT's has been included in the primary endpoint, both proximal and distal DVT's should be assessed separately.
- incidence of documented symptomatic venous thromboembolic events (PE and/or DVT's) 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.

4. SAFETY

Regarding bleedings, a method for assessing the safety of the medicinal product of interest should be used consistently across the entire development program. To this aim, validated and clinically relevant classification of bleedings should be used. Similarly to the efficacy evaluation, the adjudication of bleeding events by a central independent and blind committee of experts, using pre-specified and detailed rules of adjudication is strongly encouraged.

Bleeding should be classified as major or minor. As an example, which may vary according to the clinical situation, the following criteria for major bleeding are recommended:

- fatal bleeding
- clinically overt bleeding associated with a fall in Hb level of 20g/l or more
- clinically overt bleeding leading to transfusion of two or more units of
- packed cells or whole blood
- retroperitoneal or intracranial bleeding
- bleeding warranting treatment cessation

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

- hemoglobin plasma level, hematocrit and red cell count changes during the treatment period,
- amount of blood loss (perioperative, postoperative) quantified by an objective method,
- incidence of patients receiving transfusion of whole blood or packed red cells and transfused quantities during the treatment period. (heterologous and autologous transfusions need to be distinguished).

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

5. MAIN FEATURES OF CLINICAL TRIAL DESIGNS FOR ASSESSING DOSE-FINDING AND THERAPEUTIC COMPARATIVE TRIALS

Several medicinal products have demonstrated efficacy for preventing acute venous thomboembolic events in surgical situations. Amongst these, the efficacy and safety of heparins (including unfractionated and low molecular mass heparins) have been the most documented. The duration of treatment was usually 10 days. An application for a longer duration of treatment should be justified by the company on the basis of specific clinical studies.

In order to prevent the incorporation of bias, clinical trials should usually be double blind, starting as early in development as possible. If this is not feasible, blind evaluation of the main endpoints (efficacy and safety) by independent adjudication committees comprised of experts in the field is mandatory.

5.1 Therapeutic exploratory studies

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 should be the incidence of proximal and distal DVT's during the treatment period (see section 3.1).

5.2 Therapeutic confirmatory studies

The aim of phase III clinical development is:

- to prove that the risk benefit of the medicinal product of interest is acceptable compared to currently registered prophylactic measure that is considered the standard of medical care for the targeted indication.
- in situations when no prophylactic methods have yet been registered in the targeted indication it should be demonstrated that the medicinal product is statistically significantly more effective than placebo while the safety profile is acceptable.

The primary endpoint should be a combination of radiological and clinical endpoints (see section 3.1)

The therapeutic indication should reflect the results of the clinical trials. An extrapolation to other clinical situations should be justified by the applicant on a case by case basis.