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

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GUIDELINE ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR PROPHYLAXIS OF HIGH INTRA- AND POST-OPERATIVE THROMBOEMBOLIC RISK

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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 surgery setting.

This guideline should be read in conjunction with Directive 2001/83/EC and other pertinent elements outlined in the current and future EU and ICH guidelines and regulations, such as:

- 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)
- Guideline on clinical investigation of medicinal products for the prophylaxis of venous thromboembolic risk in non-surgical setting (CHMP/EWP/6235/04)
- One pivotal study CPMP/EWP/2330/99
- Investigation of drug interactions CPMP/EWP/560/95

The scope of this guideline is restricted to the development of medicinal products for the prophylaxis of acute venous thrombo-embolic events (VTE), i.e. deep venous thrombosis (DVT) and pulmonary embolism (PE) that involve or originate from lower limb veins.

The prevention of long-term sequelae such as post–thrombotic leg syndrome or venous thrombosis in upper extremities, is out of scope of this guideline.

1. INTRODUCTION (background)

There is evidence that routine thromboprophylaxis reduces morbidity and mortality in surgical setting in patients at risk of DVT and PE, as opposed to routine screening or a clinical diagnosis of VTE, which are both considered unreliable.

The primary aim of thromboprophylaxis, 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 DVT are considered less serious unless propagating proximally.

The rationale for use of thromboprophylaxis in surgical patients is based on:

- high prevalence of VTE intra- and post-operatively (without prophylaxis, the incidence of hospital-acquired DVT is approximately 40–60% following major orthopaedic surgery; up to one third of these thrombi involve the proximal deep veins)
- the formation of a thrombus in a deep vein predisposes patient to symptomatic DVT and PE (which may be the initial clinical manifestation of a DVT) and fatal PE,
- proven efficacy of thromboprophylaxis at preventing DVT, proximal DVT, PE and fatal PE.

The recent risk stratification to three (high-moderate-low) or to four (very high-high-moderate-low) VTE risk levels allows for the implementation of group-specific VTE prophylaxis at each risk level:

- surgery with high VTE risk such as major orthopaedic surgery of the lower limbs (e.g. elective hip or knee surgery, hip fracture) or major abdominal and cancer surgery (e.g. colorectal surgery, uterus)
- surgery with moderate VTE risk such as major soft tissue surgery of benign disease, trauma or fracture of lower extremities
- surgery with low VTE risk such as minor abdominal surgery, varicose veins surgery, knee arthroscopy, and knee ligament reconstruction

With regard to the global VTE risk (combination of the surgery-related and patient-related risks), the surgery related risk always outweighs the patient-related risk, i.e. a high VTE risk procedure will always been considered as a high global VTE risk, whatever the patient’s risk.

The vast majority of published trials have been performed in patients with high VTE risk; the knowledge about patient populations, types of surgery, choice of comparators, duration of trials and risks for bleeding is the most accurate for this risk level. Therefore, this guideline will focus on clinical development of medicinal products aimed to provide appropriate thromboprophylaxis to patients undergoing surgery with high VTE risk.

Currently recommended thromboprophylaxis treatments

Physical or mechanical prevention

The mechanical methods currently available are elastic compression (graduate elastic compression stockings, socks or wraps), intermittent pneumatic compression (IPC) devices and foot compression. If mechanical methods are offered in conjunction with antithrombotics, their use should be well balanced between the study treatments.

Prevention by drugs

The aim of antithrombotics is to prevent the formation of a venous thrombus and/or restrict its extension by acting on the mechanisms of physiological haemostasis. Most of the anticoagulants developed for the prevention of DVT act on thrombin (factor IIa) either directly (by blocking the active site either reversibly or irreversibly) or indirectly by reducing thrombin formation by inhibiting the activation of the factors involved in the coagulation cascade.

Currently prescribed thromboprophylaxis drugs for VTE are unfractionated heparins (UFH), low molecular weight heparins (LMWH), fondaparinux and vitamin K antagonists (VKA). These drugs reduce the risk of VTE by more than 60% irrespective of type of surgery. However, a risk of bleeding is specific for each type of surgery and for each clinical situation. Their use will therefore depend on assessing, in each patient population, the antithrombotic benefit versus the risk of bleeding.

2. PATIENTS CHARACTERISTICS AND SELECTION OF PATIENTS

2.1 Predisposing factors

In addition to the well-documented surgery-related risk levels for developing VTE, there are a number of factors that are considered important predisposing risk factors for VTE. These include:

- cancer (other than that to be surgically treated) and treatment for cancer (e.g. prostate cancer): 7-fold increase in risk
- history of VTE: recurrence rate 5%/year, increased by surgery
- demographic factors such as advanced age and obesity
- hypercoagulable states: deficiency of anti-thrombin, protein C or S, activated protein C resistance (e.g. factor V Leiden), antiphospholopid syndrome
- existing clinical disease states such as congestive heart failure, respiratory insufficiency, severe inflammatory diseases/infection, trauma
- iatrogenic causes such as oral contraceptives and hormone replacement therapy
- prolonged immobilisation

The risk of bleeding also varies depending upon the characteristics of the patient population; the risk/benefit of the thromboprophylactic agent may vary between and within classes of patients. The most important risks associated with an increased bleeding are age (> 75 years), small weight and renal insufficiency.

In the majority of trials performed up to now patients with VTE and/or bleeding risk were almost systematically excluded. This does not reflect clinical reality.

Therefore, it is recommended that a sufficient number of patients with high surgery-related VTE risk level and with intrinsic risk factors for VTE (i.e. cardiac disease, infection/inflammation, cancer other than that to be operated), be evaluated in clinical trials in order to permit an adequate benefit/risk assessment at the optimal dose of the drug in these sub-populations due to the heterogeneous nature of VTE predisposing factors.

In addition, a company should keep a record of patients who were considered for enrolment but were not included, e.g. a patient screening log. This information is necessary to establish that the patient population was selected without bias.

2.2 Patient Care

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 further confounded by a variety of investigator and site specific standards of care e.g., in orthopaedic surgery, type of anaesthesia (particularly neuraxial anaesthesia) cemented or cementless prosthesis, time to ambulation and modalities of physiotherapy, including mechanical prophylactic measures (i.e. graduated compression stockings, intermittent pneumatic compression devices) and the use of drugs interfering with platelet functions.

The potential for concomitant treatments (e.g. aspirin or other non-steroidal anti-inflammatory drugs (NSAIDs) 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.

2.3 Concomitant medications

In most clinical trials, both aspirin and non-steroidal anti-inflammatory drugs are frequently interrupted in patients scheduled for major orthopaedic surgery.

Meta-analyses have shown that patients receiving aspirin combined with low dose heparins have non-significant trends to increased efficacy in VTE prevention and to increased risk of bleeding. However, aspirin and other antiplatelet drugs are effective at reducing major vascular events in patients with atherosclerotic disease, e.g. myocardial infarction. Therefore, the use of aspirin should not be interrupted in patients with risk for major vascular events in spite of increased risk for bleeding. Stopping aspirin in such patients immediately prior to surgery will not reduce peri-operative bleeding (because the antiplatelet effect of aspirin lasts a week) and carries the risk that aspirin may not be re-prescribed after surgery.

NSAID are also frequently interrupted in clinical trials before major orthopaedic surgery. These drugs are necessary for general and post-operative management of patients with osteoarthritis. It is recommended that patients with NSAID be kept on this treatment as much as possible in spite of the possible increase in side effects; the lack of data on concomitant use of NSAID and thromboprophylaxis will enable proper use of these drugs in clinical practice.

3. METHODS TO ASSESS EFFICACY

3.1 Methods for diagnosing DVT

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

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

In case other diagnostic methods are considered, the relevance of such methods -especially their specificity- should be justified by the applicant.

3.2 Diagnosis of PE

Clinical signs and symptoms suggesting PE should be confirmed by perfusion/ventilation pulmonary scintigraphy including a chest x-ray or a spiral computerised tomography (recommended diagnostic methods). 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.

3.3 Dose selection and duration of treatment

Appropriate dose response studies might need to 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 post-operative thromboprophylaxis will depend of type of surgery; it may be short (e.g. 10 days) or long (e.g. 5 weeks). The following durations of thromboprophylaxis are **suggested** for:

- total hip replacement and hip fracture: 5 to 6 weeks
- major abdominal surgery due to cancer: 4 to 6 weeks
- knee surgery: 10 to 14 days
- major abdominal surgery (no cancer, e.g. for inflammatory diseases): 7 to 10 days.

The duration of trial should correspond to the recommended duration of thromboprophylaxis in each clinical situation.

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

3.4 Appropriate endpoints in therapeutic exploratory trials

An important objective will be to demonstrate that the medicinal product decreases the number of patients developing DVT within the prophylactic treatment period, the duration of which should cover the time period with an increased VTE risk. In studies aiming to show a biological activity of a new drug, the incidence of patients with **total DVT,** detected either by venography or by venous Doppler ultrasonography, might be an acceptable endpoint. Number of distal DVT (symptomatic and asymptomatic), proximal DVT and PE are recommended secondary endpoints.

3.5 Appropriate endpoints in therapeutic confirmatory trials

The choice of the primary efficacy endpoint will depend on the targeted labelling of the indication for the drug under development. Whatever the choice of the target population, the primary efficacy endpoint should have been demonstrated to be clinically relevant.

The recommended primary endpoint in therapeutic confirmatory trials should be a composite endpoint consisting of clinically relevant and objectively documented events:

- well-documented proximal DVT (asymptomatic and symptomatic)
- symptomatic and well documented non-fatal PE
- VTE related death or death due to any cause

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

The same clinically relevant events are recommended for superiority and for non-inferiority trials, except for causes of death.

In non-inferiority trials, it is generally recommended to choose an endpoint reflecting as much as possible the effect of a drug; therefore, a VTE related death (or a death considered to be due to VTE, such as fatal PE and sudden death, as autopsy findings may not be always available) is recommended.

For superiority trials, a death form any cause is recommended as a part of a composite endpoint.

All deaths must be reported. Deaths should be carefully characterised 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.

In both cases, a supportive analysis of the composite endpoint using the alternative group of deaths should be provided, i.e. VTE-related deaths for a superiority trial and all cause deaths for a non-inferiority trial.

3.6 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 total DVT (proximal and distal)
- Incidence of proximal DVT (symptomatic and asymptomatic)
- Incidence of distal DVT (symptomatic and asymptomatic)
- Incidence of PE
- VTE-related death
- Death from all causes
- Incidence of VTE (PE and / or DVT) 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. STRATEGY AND DESIGN OF CLINICAL TRIALS

4.1 Main features of clinical trials

The majority of published trials have been performed in patients with high VTE risk; the knowledge about patient populations, types of surgery, choice of comparators, duration of trials and risks for bleeding is the most accurate for this risk level. Therefore, this guideline will focus on clinical development of medicinal products aimed to provide appropriate thromboprophylaxis to patients undergoing surgery with **high risk of VTE**.

Within the high-risk level, different types of surgery (e.g. knee surgery, as opposed to hip surgery; major abdominal surgery for cancer as opposed to abdominal surgery due to other causes) have different safety profiles (bleeding), which are inherent to each type of surgery.

In addition, there may be bioavailability differences for orally administered products in patients with major abdominal surgery.

Moreover, cancer bears an increased risk for VTE itself, surgery is an additional risk factor. Patients with major abdominal surgery for cancer are considered at very high risk for VTE; they cannot be studied together with other high-risk patients, because of differences in number of VTE (as compared to e.g. hip replacement) and differences in safety profile (bleeding, mortality due to VTE or to cancer).

Therefore, separate trials are generally recommended for each clinical situation. If different types of surgery are included in the same trial (if treatment duration is the same and comparators are the same), patients should be fully stratified and powered for type of surgery.

In addition, it has been demonstrated that the same prophylactic regimen can give different efficacy results in different surgical settings. For instance, the same LMWH dose appears to be less potent in total knee replacement patients as compared with total hip replacement patients, as far as the venographic *and* symptomatic VTE are concerned (5-8).

The granted indication will always correspond to the target population and to the type of surgery performed, e.g. “thromboprophylaxis in patients (at high risk for developing VTE) undergoing hip replacement surgery”.

A larger claim, such as “prevention of VTE in patients (at high risk for developing VTE) undergoing major orthopaedic surgery”, may be granted in case of positive results from 2 trials:

- hip surgery (hip replacement and hip fracture together)(long prophylaxis trial)
- knee surgery (short prophylaxis trial)

In addition, a claim such as “prevention of VTE in patients (at high risk for developing VTE) undergoing major abdominal surgery” might be granted in case of positive results from at least one trial in major abdominal surgery due to cancer (long prophylaxis trial). The possibility or not to

extrapolate efficacy and safety data from this trial to patients with major abdominal surgery due to other causes (short prophylaxis trial) should always be discussed.

In order to prevent the incorporation of bias, clinical trials should be double blind, randomised and controlled. If this is not feasible, (different routes of administration) blind evaluation of the main endpoints (efficacy and safety) by independent adjudication committees comprised of experts in the field is mandatory.

4.2 Early studies in man

Pharmacodynamics

Pharmacodynamic trials should investigate the mechanism of action of the product and the correlation between the PK and PD in healthy subjects and in patients, by using the appropriate human models of thrombosis, in the presence of drugs known to affect haemostasis and coagulation time assays. Effect on thrombus formation, thrombin generation, on activated prothrombin time, and on ecarin clotting time should be assessed as appropriate.

Possible pharmacodynamic interactions with other relevant medicinal products such as ASA, diclofenac or clopidogrel, should also be investigated.

Pharmacokinetics

Pharmacokinetics trials should be performed in healthy volunteers and in patients (e.g. orthopaedic surgery patients) in order to obtain information on the absorption, distribution, metabolism and excretion of the product following IV, SC or oral administration.

In addition, pharmacokinetic profile of the product in development should also be studied in the following specific patient populations: patients with impaired renal function (moderate, severe), impaired liver function, obese patients, low weight (< 50 kg), and elderly (> 70 years old).

4.3 Therapeutic exploratory studies

These studies should allow choosing both the appropriate doses(s) of the medicinal product, and the appropriate timing of the initiation of treatment in relation with surgery (pre- or post-operative administration).

Before implementation of the major dose-finding studies, an open dose-ranging study might be useful to eliminate ineffective doses as well as doses associated with major bleeding.

The major dose-finding studies should test several doses of the medicinal product. The use of a placebo-control group, when ethical, is strongly recommended. 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. In high-risk patients, the use of placebo is impossible and the medicinal product should be compared to a reference product only.

Randomised, parallel group, double-blind design is recommended.

If patients with more than one type of surgery are included (e.g. hip, knee), they should be stratified according to type of surgery.

The recommended primary endpoint is incidence of total VTE (see 3.3.1). Data on proximal DVT, distal DVT and PE should also be given.

4.4 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 current best practice for prophylaxis of VTE in the target population.

For the management of patient-related risk factors (see 2.1)

For the primary efficacy endpoint (see 3.5)

4.5 Choice of comparator

The choice of comparator(s), doses and the duration of treatment will depend on surgery-related risk level, e.g. low molecular weight heparins, fondaparinux or oral vitamin K antagonists for high-risk surgery.

4.6 Studies in special populations

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

In general, the following groups might require specific evaluation.

- elderly (> 70 years)
- extremes of body weight
- renal insufficiency (moderate, severe)
- liver disease

In particular, renal insufficiency, very frequent and related to patients' age and surgery itself, increases both VTE risk and bleeding risk.

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 in special populations 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.

5. CLINICAL SAFETY EVALUATION

This will depend on the product under consideration and its potential for adverse effects, depending on its mode of action and pharmacologic 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 bleedings 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 should be classified as major or minor. Examples of major bleeding include:

- fatal bleeding
- clinically overt bleeding associated with a decrease in the haemoglobin level of more than 20 grams/l compared with the pre-randomisation level
- clinically overt bleeding leading to transfusion of two or more units of whole blood or packed cells
- critical bleeding (intracerebral, intraocular, intraspinal, pericardial, or retroperitoneal)
- bleeding warranting treatment cessation
- bleeding located at the surgical site and leading to re-operation

Nevertheless, the definition of major and minor bleeding 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 bleedings, other bleedings related parameters should be recorded during the studies e.g.:

- haemoglobin plasma level, haematocrit and red cell count changes during the treatment period, creatinine, serum protein level

- measured blood loss (peri-, post-operative) quantified by an objective method (weight of swabs and operative drapes, volumes in the suction bottles after surgery, and drain collectors on admission to the post-anaesthesia care unit and thereafter for the two post-operative days)
- calculated blood loss (peri-, post-operative) using the following formula: calculated bleeding, expressed in ml of red blood cells (RBC), haematocrit (Ht) 100% = estimated blood volume (EBV) x (preoperative Ht – day 2 Ht) + 150 ml per RBC or cell salvage unit, assuming an EBV of 70 ml/kg (men) or 65 ml/kg (women) and, respectively, 65 ml/kg and 60 ml/kg for obese men and women
- incidence of patients receiving transfusion of packed red cells and transfused quantities during the treatment period. (homologous and autologous transfusions need to be distinguished)

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

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.

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.

7. DEFINITIONS

Deep vein thrombosis (DVT) of the lower limbs is a common disease, asymptomatic, or presenting with clinical symptoms (leg pain and/or swelling); the formation of a thrombus in a deep vein predisposes patient to complications such as pulmonary thromboembolism (PE), and post-thrombotic leg syndrome (PLS).

Asymptomatic DVT is defined as DVT detected by screening with ultrasound or ascending venography.

Symptomatic DVT (leg pain and swelling) results from occlusion of a major leg vein. It requires specific investigation and treatment.

Pulmonary embolism (PE) may present as sudden death, breathlessness, faintness, collapse or chest pain. Fatal PE is under-diagnosed due to the non-specificity of symptoms and signs prior to death.

Post-thrombotic leg syndrome (PLS) (chronic leg pain, swelling, ulcers, dermatitis) is the consequence of destruction of leg vein valves by DVT.

Venous thromboembolism (VTE) is defined as DVT+/-PE.

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