EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

14 May 2012
EMA/CHMP/325170/2012 (former CPMP/EWP/707/98 Rev. 1 corr)
Committee for Medicinal Products for Human Use (CHMP)

Guideline on clinical investigation of medicinal products for prevention of venous thromboembolism (VTE) in patients undergoing high VTE-risk surgery

Draft[1]

Draft Agreed by Efficacy Working Party	04 October 2006
Adoption by CHMP for release for consultation	16 November 2006
End of consultation (deadline for comments)	31 May 2007
Agreed by Efficacy Working Party	June – October 2007
Adoption by CHMP	15 November 2007
Date for coming into effect	31 May 2008
Draft Agreed by Cardiovascular Working Party	28 March 2012
Adoption by CHMP for release for consultation	14 May 2012
Start of public consultation	30 May 2012
End of consultation (deadline for comments)	30 November 2012

This guideline replaces the Guideline on clinical investigation of medicinal products for Prophylaxis of Intra- and Post-operative Venous Thromboembolic Risk (CPMP/EWP/707/98 Rev.1 corr).

Comments should be provided using this template. The completed comments form should be sent to CVSWPSecretariat@ema.europa.eu.

Keywords	*CHMP, EMA, Guideline, Drug Evaluation, Drug Approval, Venous thromboembolic risk*

[1] Delete once the guideline is adopted.

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Guideline on clinical investigation of medicinal products for prevention of venous thromboembolism (VTE) in patients undergoing high VTE-risk surgery

Table of contents

Executive summary

This guideline is a revision of *the CHMP Guideline on clinical investigation of medicinal products for Prophylaxis of Intra- and Post-operative Venous Thromboembolic Risk (CPMP/EWP/707/98 Rev.1 corr)*. Revision 1 was intended to provide guidance for the evaluation of new medicinal products in the primary prophylaxis of high intra- and post-operative venous thrombo-embolic risk. It clarified the requirements for clinical documentation needed to support a marketing authorisation in orthopaedic and abdominal surgery setting, notably the recommended methods of diagnosing DVT, duration of treatment, the appropriate endpoints in therapeutic exploratory and therapeutic confirmatory trials, and overall strategy of development on thromboprophylactic products in this setting. This second revision includes an updated definition of major bleeding and its assessment. It also proposes a definition for clinically relevant minor bleeding and inclusion of other secondary endpoints related to the reporting of surgical blood loss, blood transfusions, wound complications, functional outcomes, hepatic and cardiovascular events.

1. Introduction (background)

There is evidence that routine thromboprophylaxis reduces morbidity and mortality in surgical setting in patients at risk of DVT and PE [1-4], 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 as less serious [5], but may in some circumstances propagate proximally.

A secondary aim of thromboprophylaxis is to prevent or limit the occurrence of the post thrombotic syndrome.

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 asymptomatic DVT [assessed by venography] 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 risk stratification to three (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, uterine, ovarian surgery)
- 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, knee ligament reconstruction

With regard to the global VTE risk (combination of the surgery-related and patient-related risks), the surgery related risk in principle 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

Early mobilisation and elastic compression (graduate elastic compression stockings, socks or wraps) are standard non-pharmacological measures to be offered to all surgical patients at risk of VTE. If mechanical methods like intermittent pneumatic compression (IPC) devices and venous foot pump (VFP) 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, mainly factor Xa.

2. Scope

The scope of this guideline is restricted to the development of medicinal products for the prophylaxis of acute venous thromboembolic events (VTE), i.e., deep venous thrombosis (DVT) and pulmonary embolism (PE) that involve or originate from lower limb veins in patients undergoing surgery at high risk of VTE.

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.

3. Legal basis

This guideline is intended to provide guidance for the evaluation of new medicinal products in the primary prophylaxis of venous thromboembolic risk in the surgery setting.

This guideline should be read in conjunction with the introduction and general principles of the Annex I to the Directive 2001/83/EC as amended, 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, CPMP/ICH/378/95)
- Statistical Principles for Clinical Trials (ICH E9, CPMP/ICH/363/96)
- Choice of Control Group in Clinical Trials (ICH E10, CPMP/ICH/364/96)

- Population Exposure: The Extent of Population Exposure to Assess Clinical Safety (ICH E1, CPMP/ICH/375/95)
- Studies in Support of Special Populations: Geriatrics (ICH E7 CHMP/ICH/379/95) and related Q&A document (EMA/CHMP/ICH/604661/2009)
- Guideline on clinical investigation of medicinal products for the prophylaxis of venous thromboembolic risk in non-surgical setting (CHMP/EWP/6235/04)
- Points to Consider on Application with 1. Meta-analyses; 2. One Pivotal study CPMP/EWP/2330/99
- Investigation of drug interactions (CPMP/EWP/560/95)
- Reflection paper Investigation of gender differences in cardiovascular diseases (EMEA/CHMP/EWP/498145/2006)
- Regulation (EC) No 1901/2006 as amended (the 'Paediatric Regulation')

4. Main guideline text

4.1. Patients characteristics and selection of patients

4.1.1. 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 antithrombin, protein C or S, activated protein C resistance (e.g. factor V Leiden), antiphospholipid 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. age, 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. Benefit/risk assessment in these sub-populations should be consistent with the overall results.

It is important to establish that the patient population was selected without bias. One approach could be a record of patients who were considered for enrolment but were not included, e.g. a patient screening log.

4.1.2. 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 anesthesia) 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 [NSAID]) 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.

4.1.3. 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 are responsible for an 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, it is not necessary that aspirin 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). If necessary, aspirin might be interrupted in patients with very high bleeding risk. This remains at the discretion of the physician. It is important to ensure that aspirin 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.

4.2. Methods to assess efficacy

4.2.1. Methods for diagnosing deep venous thrombosis

DVT may be diagnosed by bilateral ascending contrast venography, duplex ultrasound or colour duplex ultrasound.

Venography remains the gold standard for diagnosing all DVT (distal and proximal). Duplex ultrasound (compression ultrasound coupled with doppler) and colour duplex ultrasound have an excellent sensitivity and specificity for proximal DVT and symptomatic distal DVT, but less so for asymptomatic distal DVT. The techniques should be standardised and the trial should use an independent, blinded centralized adjudication process.

The choice of DVT diagnosing method will be partly influenced by the choice of the primary composite endpoint in therapeutic confirmatory trials (see sections 4.2.4 and 4.2.5). The timing of the diagnostic modality to establish DVT is dependent on the primary end point in the confirmatory trials and should take into account any impact on the subsequent maintenance of blinded follow up.

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.

4.2.2. Diagnosis of pulmonary embolism

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.

4.2.3. 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. 4 to 5 weeks). The following durations of thromboprophylaxis are suggested for:

- total hip replacement and hip fracture: up to 5 weeks after surgery
- high-risk general surgery (abdominal surgery due to cancer, history of VTE): up to 4 weeks
- knee surgery: 10 to 14 days
- major abdominal surgery (no cancer, e.g. for inflammatory diseases): 7 to 10 days.

4.2.4. Appropriate endpoints in therapeutic exploratory trials

An important objective will be to demonstrate that the medicinal product decreases the number of patients developing VTE within the prophylactic treatment period, the duration of which should cover the time period with an increased VTE risk.

In therapeutic exploratory trials, the most sensitive endpoint is considered to be **total VTE,** defined as the composite of:

- total DVT (proximal and/or distal; asymptomatic or symptomatic, detected by venography and/or duplex or colour duplex ultrasound)
- symptomatic non-fatal PE documented by objective methods
- VTE-related death.

The outcome "VTE-related death" may include fatal PE documented by autopsy as well as deaths in which a fatal PE cannot be ruled out.

Secondary endpoints may include the components of the main endpoint (total DVT, proximal DVT, distal DVT, non-fatal PE, VTE-related death).

4.2.5. 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.

As the primary aim of thromboprophylaxis is to prevent PE (fatal and non fatal), which is usually resulting from proximal DVT, the most clinically relevant endpoint is considered to be a composite endpoint consisting of clinically relevant and objectively documented events:

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

In addition, as symptomatic distal DVT are clinically relevant (patients with symptomatic distal DVT are treated) and can be easily objectively documented, they might be a part of the composite primary endpoint.

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.

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 as part of a composite endpoint.

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

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 and detailed in the adjudication manual of the clinical event committee. 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.

The use of a clinically relevant composite primary endpoint (excluding asymptomatic distal DVT) is mandatory for new medicinal products under development for thromboprophylaxis of patients undergoing high-risk surgery in at least one active comparative trial in the recommended patient population (see section 4.3 Strategy and design of clinical trials).

4.2.6. Secondary efficacy endpoints

These endpoints (if not part of the primary endpoint) 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.

4.3. Strategy and design of clinical trials

4.3.1. 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 VTE risk.**

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. It has been demonstrated that the same prophylactic regimen has 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 [6-9].

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

Moreover, cancer itself bears an increased risk for VTE, surgery is an additional risk factor. Patients with major abdominal surgery for cancer have high risk for VTE; they cannot be studied together with other patients undergoing abdominal surgery, because of differences in number of VTE 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, patients should be fully stratified and powered for type of surgery.

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-term prophylaxis trial)
- knee surgery (short term prophylaxis trial)

As previously stated (see section 4.2.5), it is recommended to perform at least one comparative trial with the most clinically relevant composite primary endpoint (excluding asymptomatic distal DVT); the recommended study population are patients with hip surgery (hip fracture and hip replacement). Patients with hip fractures should be well represented in the trial as they are frequently elderly, frail, overweight or underweight patients, with renal insufficiency and high risk for bleeding. In addition, this population has the highest number of clinically relevant events.

Once acceptable efficacy and safety of a new product (as compared to the adequately dosed reference treatment regimen) have been convincingly demonstrated in the recommended patient population and using the most clinically relevant primary endpoint, a less stringent primary endpoint, such as a composite of total DVT (proximal and distal), PE and death, might be used in the subsequent product development in orthopaedic surgery, e.g. in patients with knee surgery.

A choice of less stringent endpoint is based on the existence of a large efficacy and safety database acquired form the study done with the most clinically relevant endpoint. All clinically relevant parts of the composite endpoint (especially proximal DVT, PE and deaths) should support the efficacy of the product in the presence of an acceptable safety profile.

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 patients with major abdominal surgery due to cancer (long prophylaxis trial). The possibility to extrapolate efficacy and safety data from this trial to patients with major abdominal surgery due to other causes (short prophylaxis trial) might be accepted if properly justified.

As in major orthopaedic surgery, a clinically relevant composite endpoint (excluding asymptomatic distal DVT) is mandatory in patients undergoing major abdominal surgery due to cancer. However, feasibility of such a trial may be discussed with the competent authorities, in view of the anticipated decrease in the number of clinically relevant events due to prolongation of thromboprophylaxis from 10 to 30 days. Provided the product has a comparable or better safety profile than the reference treatment, and sufficient efficacy and safety data has been generated in orthopaedic patients, a less stringent endpoint including distal DVT may be acceptable.

In order to prevent the incorporation of bias, all clinical trials should be double blind, randomized and active 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.

Timing of assessments: the assessment of efficacy and safety should be made in a harmonised way with the duration of treatment (see section 4.2.3). Normally, screening tests for diagnosing

asymptomatic DVT and/or PE should be performed within 24 hours after the last dose of study treatment, or earlier if patient develops symptoms during study treatment. Safety outcomes should be assessed separately on-treatment and during follow-up (at least 1 month; usually 3 months).

4.3.2. 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 partial thromboplastin time (aPTT) and on ecarin clotting time should be assessed as appropriate.

Possible pharmacodynamic interactions with other relevant medicinal products such as antiplatelet drugs and NSAID, 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 (> 75 years old).

4.3.3. 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-op or post-op 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 excessive bleeding risk.

The major dose-finding studies should test several doses of the medicinal product. The use of an active control group is encouraged in order to “calibrate” the efficacy and safety observations made on the compound under development.

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 section 4.2.4). Data on proximal DVT, distal DVT and PE should also be given.

4.3.4. 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. Since the use of thromboprophylaxis in high-risk VTE surgery is well established, confirmatory studies are expected to show non-inferiority or superiority versus an appropriate active comparator (see section 4.3.5).

For the management of patient-related risk factors, see section 4.1.1.

For the choice of primary efficacy endpoint, see sections 4.2.5 and 4.3.1.

4.3.5. Choice of comparator

Traditionally, low molecular weight heparins (e.g.: enoxaparin) have been chosen as comparator in VTE prophylaxis trials. However, other antithrombotics indicated for VTE prophylaxis may be acceptable as comparators if appropriately justified. In patients at high risk of VTE, the use of placebo may be unethical and therefore it is not recommended.

4.3.6. 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, with dose adaptation justification when appropriate:

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

Regarding the elderly, it is important to determine whether or not the pharmacokinetic behaviour of the drug in this population is different from that in younger adults. A reasonable number of patients >65 years and >75 years should be included in the therapeutic confirmatory studies.

In particular, renal insufficiency is a risk factor for both VTE and bleeding, being common in elderly patients undergoing major surgery

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.

4.4. Clinical Safety Evaluation

4.4.1. Bleeding events and related parameters

Bleeding is the most important safety issue with antithrombotics. 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.

In dose-finding studies, the use of a sensitive safety endpoint to assess bleeding risk, like the composite of major and clinically relevant non-major bleeding, is recommended. In pivotal trials, the recommended primary safety endpoint is major bleeding.

The description of the severity (i.e: life threatening versus non-life threatening major bleed), localisation (i.e.: surgical site, extra-surgical site including intracranial, gastrointestinal, etc.) and temporal pattern (i.e.: time-to-event analysis) is encouraged.

Bleeding definitions and related parameters recommended for use in clinical trials for the prevention of VTE in patients undergoing high VTE-risk surgery are given below.

Major bleeding

Major bleeding [10, 11], is defined, as a bleeding event that meets at least one of the following criteria:

- fatal bleeding
- critical bleeding (intracranial, intraocular, intraspinal, pericardial, retroperitoneal, in a non-operated joint, or intramuscular with compartment syndrome)
- clinically overt bleeding (at surgical or extrasurgical site) associated with a decrease in the haemoglobin level of more than 2 g/dL (20 g/l; 1.24 mmol/L) compared with the pre-randomisation level
- clinically overt bleeding (at surgical or extrasurgical site) leading to transfusion of two or more units of whole blood or packed cells
- bleeding located at the surgical site and leading to re-operation or to any unusual medical intervention or procedure for relief (e.g. draining or puncture of an haematoma at the surgical site, transfer to an ICU or emergency room)

It is strongly recommended to use the above definition for the primary safety outcome in pivotal trials. The exclusion of wound bleeding events is strongly discouraged, since these events comprise about 80% of all major bleeds in major orthopaedic surgery and therefore, their exclusion may lead to an unacceptable underestimation of bleeding risk [12].

Bleeding warranting treatment cessation is no longer considered as a sole criterion for qualifying a bleeding as major, because the decision for treatment cessation may be subjective and influenced by a variety of factors other than the severity of bleeding [11]. However, the criterion of “treatment cessation” is still considered valid to qualify a bleed as “clinically relevant non-major bleeding”, because it may be considered as an action taken to control bleed (see below).

The use of other major bleeding definitions (in addition to the one included above) for the purpose of sensitivity analyses is optional.

In order to describe bleeding severity, major bleedings may be further sub-classified as **life threatening** [13, 14] if they meet at least one of the following criteria:

- Fatal, symptomatic intracranial bleed
- Reduction in hemoglobin of at least 5 g/dL
- Transfusion of at least 4 units of blood or packed cells, associated with substantial hypotension requiring the use of intravenous inotropic agents
- Necessitated surgical intervention

All the remaining major bleeds may be considered as non-life threatening major bleeds.

Clinically relevant non-major bleeding

Clinically relevant non-major bleeding [11,15] is defined as any clinically overt bleeding that does not meet the criteria for major bleed but requires medical attention (e.g.: hospitalisation, medical treatment for bleeding) and/or a change in antithrombotic therapy (including discontinuation or down-titration of study drug) and/or any other bleeding type considered to have clinical consequences for a patient.

Examples of clinically relevant non-major bleed are: multiple-source bleeding; spontaneous hematoma >25 cm^2, or > 100 cm^2 if there was a traumatic cause; intramuscular hematoma documented by ultrasonography without compartment syndrome; excessive wound hematoma not requiring draining or puncture; macroscopic hematuria (spontaneous or lasting >24 h if associated with an intervention); epistaxis or gingival bleeding that requires tamponade or other medical intervention, or bleeding after venipuncture for >5 min; hemoptysis, hematemesis or spontaneous rectal bleeding requiring endoscopy or other medical intervention.

Other non-major bleedings

Other non-major bleedings include other overt bleeding events that do not meet the criteria for major bleed or clinically relevant non-major bleed (e.g.: epistaxis that does not require medical attention or change in antithrombotic therapy).

Composite bleeding endpoints of interest

The use of the following composite bleeding endpoints is recommended:

- **Clinically relevant bleeding:** defined as the rate of patients experiencing at least one major bleeding and/or a clinically relevant non-major bleeding.
- **Non-major bleeding:** defined as the rate of patients experiencing at least one clinically relevant non-major bleeding or other non-major bleeding.
- **Total bleeding:** defined as the rate of patients experiencing at least one major bleeding, clinically relevant non-major bleeding or other non-major bleeding.

Report and collection of bleeding events and related parameters

The population included in the assessment of bleeding events should correspond with those subjects who have received at least one dose of the study drug (either active or placebo) (i.e.: the safety population).

The period for collection of these data should be identical in all treatment groups, starting at the time of the administration of the first dose of study drug (either active or placebo) in any of the treatment groups, until the antithrombotic effect of study drugs is not detectable, and after study drugs have been cleared from plasma.

Other parameters related to surgery

As support for the conclusions drawn from the main safety criteria, other bleedings related parameters are recommended to be recorded during the studies e.g.:

- **Laboratory parameters:** haemoglobin plasma level, haematocrit and red cell count changes during the treatment period,
- **Operative blood loss (mL)** quantified by an objective method (weight of swabs and operative drapes, volumes in the suction bottles after surgery).

- **Post-operative wound drainage (mL)** quantified by and objective method (drain collectors on admission to the post-anaesthesia care unit and thereafter for the two postoperative days).
- **Patients with post-operative drain (n, %)**
- **Calculated blood loss (peri-operative, postoperative)** 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.
- **Bleeding index (mean, ±SD)** calculated in each patient as the number of units of packed red cells or whole blood transfused plus the haemoglobin values pre-randomisation minus the haemoglobin values at the end of treatment period.
- **Patients with bleeding index ≥ 2** at the end of treatment period relative to haemoglobin pre-randomisation levels (n, %).
- **Patients receiving transfusion of packed red cells (n, %)** (homologous and autologous transfusions need to be distinguished).
- **Transfusion volume (mL; mean, ±SD)** and **transfusion units (U; mean, ±SD)** during the treatment period (homologous and autologous transfusions need to be distinguished).

Triggers for blood transfusion should be clearly defined in the study protocol.

Wound complications

It is encouraged the collection of the number and percentage of patients with wound complications in the safety population. These complications should be further detailed as:

- **Infectious:** prosthetic infection, wound infection.
- **Non-Infectious:** wound bleeding, wound hematoma, wound secretion.

The time to complete wound healing may also be of interest.

Functional outcomes

As a safety measure, it should be investigated a potential impact of the type of thromboprophylaxis in functional outcomes. These are particularly relevant in the older population. In the case of major orthopaedic surgery, the Harris Hip Score [16] and the Knee Society score [17] are clinician completed functional scores that may be useful to investigate the potential effect of thromboprophylaxis (mediated by its effect on VTE/bleeding) on patient's and prosthetic functionality. This assessment should be made at least at baseline and at last follow-up study visit (usually at 3 months).

4.4.2. Other events of interest

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, renal and liver function parameters, hypercoagulability markers to assess a possible rebound hypercoagulation after treatment cessation, etc.) that should be considered for incorporation into the entire development programme.

In particular, arterial thromboembolic events (ATE), such as stroke and acute coronary syndromes, are important adverse events following orthopaedic surgery [18]. The composite endpoint of stroke, MI,

unstable angina and cardiovascular deaths, as well as the individual components, are recommended as secondary safety endpoints. These events should be collected during and after treatment to investigate a possible rebound phenomenon.

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.

4.5. 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.

Description of terms

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).

Proximal DVT is defined as DVT in the popliteal vein and/or higher (femoral vein, common femoral vein, iliac vein, vena cava)

Distal DVT (calf DVT) is defined as DVT in at least 1 of the 3 major paired veins (posterior tibial, anterior tibial, peroneal) in the calf, below the popliteal vein.

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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