European Medicines Agency
Evaluation of Medicines for Human Use

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CHMP ASSESSMENT REPORT

FOR

Xarelto

International Nonproprietary Name: rivaroxaban

Procedure No. EMEA/H/C/000944

Assessment Report as adopted by the CHMP with
all information of a commercially confidential nature deleted.

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1. BACKGROUND INFORMATION ON THE PROCEDURE

1.1 Submission of the dossier

The applicant Bayer HealthCare AG submitted on 31 October 2007 an application for Marketing Authorisation to the European Medicines Agency (EMEA) for Xarelto, through the centralised procedure under Article 3 (2) (a) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMEA/CHMP on 26 April 2007.
The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The application submitted is a complete dossier composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies)

Scientific Advice:
The applicant received Scientific Advice from the CHMP on 25 July 2003 and follow-up Scientific Advice on 16 September 2005. The Scientific Advice pertained to clinical aspects of the dossier.

Licensing status:
The product was not licensed in any country at the time of submission of the application.

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: Bengt Ljungberg Co-Rapporteur: Karl Broich

1.2 Steps taken for the assessment of the product

- The application was received by the EMEA on 31 October 2007.
- The procedure started on 23 November 2007.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 8 February 2008. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 8 February 2008.
- During the meeting on 17-19 March 2008, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 19 March 2008.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 25 April 2008.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 5 June 2008.
- During the CHMP meeting on 23-26 June 2008, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 2 July 2008 and additional clarifications on 4 July 2008
- The Rapporteurs circulated the Joint Assessment Report on 10 July 2008.
- The applicant submitted additional clarifications on 15 July 2008
- The Rapporteurs circulated the Joint Assessment Report on 18 July 2008.
- During the meeting on 21-24 July 2008, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a

Marketing Authorisation to Xarelto on 24 July 2007. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 23 July 2008

- The CHMP opinions were forwarded in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision on 30 September 2008.

2 SCIENTIFIC DISCUSSION

2.1 Introduction

Venous thromboembolism (VTE) including deep vein thrombosis (DVT) and pulmonary embolism (PE) is a common cause of cardiovascular mortality and morbidity. Subjects undergoing major orthopaedic surgery, which includes hip and knee arthroplasty and hip-fracture repair, represent a group that is at particularly high risk for VTE, especially patients with risk factors (age >60 years, cancer, prior VTE). Some uncertainty exists for what the spontaneous VTE rates would be without prophylaxis when up-to date surgical technique, early mobilisation and other non-pharmacological prophylactic measures are undertaken. It may be that some estimations, based on historical data, overestimate the current risks but it is generally accepted that VTE risks in these patients remain high. Placebo-controlled trials in such populations would hardly be regarded as acceptable. Estimations fetched from the literature and cited by the Applicant are that calf vein thrombi, proximal DVT, clinical PE and fatal PE would be seen in 40-80%, 10-20%, 4-10% and 0.2-5% in such a population, respectively.
Thus, routine thromboprophylaxis has been the standard of care for more than 20 years in subjects at moderate and high risk for thromboembolism.
The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy (2004), an internationally recognised guidance document based on all available data and compiled by leading experts made the following major recommendations for the population targeted for Xarelto (strength of recommendations included within brackets):
Elective hip arthroplasty, elective knee arthroplasty, and hip-fracture surgery: (1) low-molecular weight heparin (LMWH, (2) fondaparinux, or (3) dose-adjusted vitamin K antagonist (VKA) (Grade 1A) for at least 10 days (Grade 1A).
Hip-fracture surgery: (1) fondaparinux (Grade 1A), (2) LMWH (Grade 1C+), (3) dose-adjusted VKA (Grade 2B), or (4) LDUH (Grade 1B) for at least 10 days (Grade 1A).
For subjects undergoing elective hip arthroplasty and hip-fracture surgery, an extended prophylaxis for up to 28 to 35 days after surgery is recommended (Grade 1A).
Low-dose unfractionated heparin (LDUH) is not recommended as the only method of thromboprophylaxis in subjects undergoing hip or knee arthroplasty. LDUH, however, is recommended in subjects with hip-fracture surgery.
In Europe LMWH or fondaparinux are probably the prophylactic agents that are most commonly used in these patients, also in hip fracture patients. VKA is probably used for prophylactic purposes in surgery to a smaller extent that in US.
LMWH provides effective and safe VTE prophylaxis; however LMWH needs to be administered subcutaneously and may trigger heparin-induced thrombocytopenia (HIT) type II which is a rare but serious complication.

2.2 Quality aspects

Introduction

Xarelto contains rivaroxaban as the active substance. It is presented as immediate-release film-coated tablet containing 10 mg of rivaroxaban for oral use.

Other ingredients in the core tablet include cellulose microcrystalline, croscarmellose sodium, hypromellose 5 cp, lactose monohydrate, magnesium stearate and sodium laurilsulfate. The film coating contains ferric oxide red, hypromellose 15 cp, macrogol 3350 and titanium dioxide

The tablets are packaged in thermoformed polypropylene or PVC/PVDC blisters with aluminium backing foil.

Active Substance

The chemical name of Rivaroxaban is 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxzolidin-5-yl}methyl)-2-thiophene-carboxamide. It is a white to yellowish powder with a molecular weight of 435.89. The empirical formula and the relative molecular mass of rivaroxaban have been confirmed by elementary analysis and mass spectrometry. The structure has been confirmed with spectral data: IR, UV-VIS, ^{1}H-NMR, ^{13}C-NMR, mass spectrometry and elementary analysis. The 1,3-oxazolidin ring system has in position 5 a chiral carbon-atom with (*S*) configuration. Single-crystal x-ray structural analysis confirms the S configuration of the molecule

Rivaroxaban is only slightly soluble in organic solvents (e.g. acetone, polyethylene glycol 400) and is practically insoluble in water and aqueous media with pH 1 – 9 (pH-independent 5 - 7 mg/L are soluble at 25 °C). The partition coefficient in octanol / water (log $P_{o/w}$) is 1.5.

Rivaroxaban has been tested for polymorphism and pseudo-polymorphism according to the ICH Q6A guideline (decision tree 4). Rivaroxaban crystallizes in three polymorphs. Polymorph I is the thermodynamically stable one and has been used in all tablet formulations during clinical development and will be used in the commercial product. The identity of polymorph I is routinely controlled by Raman spectroscopy at release.

- Manufacture

Rivaroxaban is synthesised using a five-step synthetic process using 4-(4-nitrophenyl)-3-morpholinone as a starting material. Three key intermediates must be synthesised, which are then used in the reaction to form the active substance. After re-crystallization of rivaroxaban crude, the material is micronised.

The route of synthesis is sufficiently described, and the main steps in the synthesis are adequately monitored during the reaction. Based on batch analysis data adequate specifications have been set to control the quality of the starting materials, solvents and reagents, and isolated intermediates.

Eighteen process impurities originating from the starting materials and the synthetic process have been identified. The origin of each impurity has been discussed and the structure of each impurity has been described based on spectral analysis data (NMR and spectrometry). In practice, only 3 impurities (acetoxamide and bis-oxamine-urea and triamide) and enantiomeric purity are monitored in batch analysis. No single structurally known organic impurity is limited above the limit of max.0.15%, which would require specific toxicological qualification.

The solvents used in the synthesis have been shown to be efficiently removed during the purification and drying operations and appropriate specifications have been set.

- Specification

The active substance specification includes tests for appearance, colour of solution, identification (IR, high performance liquid chromatography (HPLC), assay (HPLC), enantiomeric purity, polymorph I (Raman spectra), particle size (laser diffraction), related impurities (HPLC), residual solvents (GC), water content (Karl-Fischer), sulphated ash (Ph. Eur), heavy metals (Ph. Eur) and microbial purity (Ph. Eur). The analytical methods not described in Ph.Eur. have been sufficiently validated to meet the general requirements of the ICH guideline Q2R, Validation of Analytical Procedures: Test and Methodology.

The acceptance criteria in the active substance specifications have been set in accordance with ICH Q6A and are based on batch analyses of three representative pilot batches manufactured using the process described intended for marketing and 29 preclinical, clinical and stability batches. All results comply with the specification and demonstrate consistent quality of the batches produced.

- Stability

Stability data have been provided for three batches of the active substance stored at 25 °C / 60 % RH for 18 months and at 40 °C /75 % RH for six months.

The parameters studied were appearance (material, colour), colour of solution, polymorphism, particle size, enantiomeric purity, organic impurities, assay and water content using the analytical test methods intended for the release of the active substance, which have been shown to be stability indicating. In all cases the results met the predefined quality conditions set at the time of the testing. There was no degradation, or increase in the water content and no trends were identified.

Additional stability studies have been performed under stress conditions (thermal, hydrolytic and oxidative stress). The results of these studies show that rivaroxaban is a very stable substance with regards to thermal conditions and sufficiently stable with regards to hydrolytic stress.

The photostability of the active substance was tested according to the requirements of ICH Q1B. The results have shown that the active substance, when in solid state, is stable with regards to the influence of light and therefore there is no need to take any packaging and storage precautions against light.

Medicinal Product

- Pharmaceutical Development

The development objective was to provide a small size immediate release tablet formulation of rivaroxaban. The active substance is practically insoluble in water and it has a high permeability as shown by the results of a validated Caco-2 assay. Therefore it could be classified as a Class II substance in the Biopharmaceutics Classification System (low solubility, high permeability).
The problem of the low solubility of the active substance is addressed by reducing its particle size with micronisation to increase the particle surface area and thus facilitate dissolution. Dissolution profiles obtained on micronised batches of rivaroxaban were compared to non-micronised (crystalline) ones and the results support the need for micronisation of the active substance. When comparing the dissolution kinetics of micronised active substance within the specified limits of particle size distribution (e.g. X90 < 15 μm), significant differences of dissolution kinetics can not be observed.

For the formulation development well-known standard excipients that are often used in immediate release tablet formulations were employed. Microcrystalline cellulose and lactose monohydrate act as fillers, croscarmellose sodium as a disintegrant, hypromellose 5 cp as a binder, sodium laurilsulfate as a wetting agent and magnesium stearate as a lubricant. Lactose monohydrate is produced from milk from healthy animals in the same conditions as milk collected for human consumption and the magnesium stearate used is of vegetable origin only.

A comprehensive discussion on process development has been provided by the applicant. A standard fluid bed granulation process has been developed, followed by final mixing, tabletting and film-coating. The impact of manufacturing process parameters on target properties of the final dosage form, such as tablet hardness, disintegration, dissolution, content uniformity and stability has been investigated during development and scale-up and appropriate operating ranges have been set to ensure that the finished product is of the intended quality. The tablet composition and operating principles of all parts of the manufacturing process were not changed during scale-up.
The tablet dissolution rate is a critical quality attribute of the product and is influenced by active substance particle size. Therefore a discriminating dissolution test method has been developed for the release of the product. The dissolution test is performed in an acetate buffer of pH 4.5. Under these conditions the tablets show nearly complete dissolution (> 80 %) within 30 minutes meeting the requirements of the Ph.Eur. It has been shown that the developed dissolution test is able to discriminate between tablets containing different particle sizes of the active substance. A series of other properties of Rivaroxaban tablets that could potentially alter the dissolution profile and the in-vivo bioavailability were also investigated and the suitability of the test method to differentiate between batches was evaluated. The aspects that were challenged included the influence of disintegrant; granulation time; blending time; addition of wetting agent; accelerated stability testing and compression force. In all cases the discriminatory power of the dissolution test was sufficiently demonstrated.
The relevance of the specifications set for the active substance particle size distribution has been confirmed by *in vivo* studies in dogs showing that the oral absorption is independent on API particle size after administration of tablets manufactured with API within the proposed specification limits.
Different product formulations have been used in the early studies. However bioequivalence between the clinical trial formulations and the one intended for marketing has been demonstrated.

Rivaroxaban coated tablet 10 mg are packaged in PP- or PVC-aluminium blister. The immediate packaging materials are commonly used for these types of formulations and complies with

Ph. Eur. requirements. The stability studies indicate that the primary packaging is suitable for maintaining drug product quality.

- Manufacture of the Product

The manufacturing process is a standard process for these kinds of formulations and consists of the following main steps: fluidised-bed granulation, mixing, tabletting and film-coating. All critical process parameters have been identified and controlled by appropriate in process controls.
Although the proposed manufacturing process has not been validated at commercial scale, the batch analysis data collected for five pilot batches and three production scale batches, the established in process controls and the fact that the process is standard and well-characterised provide sufficient grounds to conclude that it is sufficiently robust and can reproducibly produce finished product of consistent quality complying with the approved specification. In addition the applicant has committed to perform the validation with three consecutive commercial scale batches in accordance with the approved validation protocol as a post approval commitment.

- Product Specification

The specification for the finished product at release and shelf life includes tests for appearance, identification (TLC, NIR and HPLC), assay (HPLC), dissolution (Ph. Eur. Paddle apparatus), uniformity of dosage units (Ph.Eur), impurities and microbial purity (Ph. Eur.).

The specification and control tests applied for the finished product at time of release and throughout the life of the product, are in compliance with general pharmacopoeial standards (including Ph Eur) and ICH guidelines (Q3B and Q6A). The specifications for release and throughout shelf life are identical except uniformity of content and identification. These parameters will only be tested at release.

Batch analysis data from 5 pilot scale stability and 3 commercial scale batches have been presented. All batches met the test limits as defined in the release specification and test methodology valid at the time of batch release.

- Stability of the Product

Stability studies were carried out on 3 pilot scale batches of tablets according to the ICH requirements. Samples were stored at 25°C/60 % RH and 30°C/75 % RH for 24 months and in 45°C/75 % RH for 6 months.

Additional stability data have been provided from thermal stress test conditions at 60 °C and 80 °C and high humidity stress test conditions (25°C / 60 % RH, 25 °C / 80 % RH, 30 °C / 75 % RH, 40 °C / 75 % RH) in open HDPE bottles for 12 months. Furthermore, bulk stability data at 25 °C / 60 % RH, 30° C / 75 % RH, and 45 °C / 75 % RH, and photostability data from studies performed in accordance with ICH requirements have been provided.

The parameters tested were appearance, assay, degradation products, dissolution, hardness, disintegration, water and microbial purity (at selected time points). The methods used were the same as those used at release and are stability indicating.

The results of the accelerated and long term stability studies show a slight increase in water to an equilibrium state leading to a slight decrease in hardness. However in all cases the hardness results were within the acceptable ranges. No trend and no variability were observed in any of the other tested parameters.

The results from the stress studies show that there is no formation or increase of any of the known by-products of the active substance or any unknown compound. In addition the results of the photostability studies demonstrate that both the uncoated and coated tablets are stable upon exposure to light. Therefore there is no need to introduce any storage or transport restrictions in the SPC.

In conclusion the stability results presented were satisfactory and support the proposed shelf life for the commercially packaged product under the conditions specified in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

The quality of Xarelto is adequately established. In general, satisfactory chemical and pharmaceutical documentation has been submitted for marketing authorization. There are no major deviations from EU and ICH requirements.

The active substance is well characterised and documented. It is a class II substance in the BCS classification system. Its low aqueous solubility is overcome by reducing the particle size with micronisation. Appropriate limits have been included in the active substance specifications to monitor the particle size and size distribution. Moreover the release of the active from the finished product is controlled routinely with a discriminatory dissolution test. The excipients are commonly used in these types of formulations and comply with Ph. Eur. requirements. The packaging material is commonly used and well documented. The manufacturing process of the finished product is a standard granulation, tabletting and coating process that has been adequately described. Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.

2.3 Non-clinical aspects

Introduction

Rivaroxaban is a potent, selective, orally active direct inhibitor of the activated serine protease Factor X (FXa), which plays a central role in the blood coagulation. The agent acts at the convergence point of the intrinsic and extrinsic coagulation pathways. FXa catalyses the conversion of prothrombin to thrombin, which then results in diminishing of thrombin-mediated activation of coagulation. Thus, inhibition of FXa is believed to be an effective strategy for the prevention of both arterial and venous thrombosis.

The non-clinical programme documentation for rivaroxaban is comprehensive and extensive, and provides a good characterisation of the pharmacological properties of the product. It includes investigations on primary and secondary pharmacology, characterisation of potential pharmacodynamic interactions between rivaroxaban and other antithrombotic drugs with a special focus on antithrombotic efficacy and potential risk of bleeding.

The toxicological and toxicokinetic profile of rivaroxaban was characterised in a comprehensive program, including studies to investigate the systemic toxicity as well as exaggerated pharmacodynamic effects after single and repeated administration, reproductive toxicity studies, genotoxicity studies and studies addressing specific toxicity issues.

All pivotal toxicity studies and most safety pharmacology studies were performed in accordance with Good Laboratory Practise (GLP).

Pharmacology

- Primary pharmacodynamics

The results of receptor binding and enzyme inhibition screens adequately demonstrate that rivaroxaban is a selective FXa inhibitor, and that pharmacological effects due to interaction with unrelated receptors/enzymes are unlikely.

In the *in vitro* investigations, rivaroxaban competitively inhibited human FXa (K_i 0.4 nM) with a rapid onset of the activity and >10,000-fold greater selectivity compared to other serine proteases. Rivaroxaban is a reversible inhibitor, with a mean half-lifetime of 200s. Rivaroxaban showed a low IC_{50} in the prothrombinase assay (2.1 nM), and demonstrated anticoagulant effects in human plasma, doubling prothrombin time (PT) and activated partial thromboplastin time (aPTT) at 0.23 and 0.69 µM, respectively. Species differences in FXa inhibition were also discussed. Rivaroxaban inhibited endogenous FXa more potently in human (IC_{50} 21 nM), rabbit (IC_{50} 21 nM) and dog (IC_{50} 114 nM) plasma than in rat plasma (IC_{50} 290 nM). These species differences are likely to be the result of differences both in plasma binding and in the K_i of rivaroxaban for FXa. Nevertheless, the rat appears to be a sensitive species, which was seen in *in vivo.*

When given as prophylaxis *in vivo*, rivaroxaban produced antithrombotic activity in a dose-dependent manner in a variety of well-characterised experimental animal models. Antithrombotic activity was showed in venous (platelet-poor, fibrin-rich) and arterial (platelet-rich, fibrin-poor) thrombosis models in rats, in mice and in rabbits. Intravenously administered rivaroxaban (ED_{50} 0.6-1 mg/kg *iv*) in the

arterial thrombosis model tended to exhibit greater potency than the comparator enoxaparin (ED_{50} 1-4 mg/kg *iv*). Although lower doses of both rivaroxaban (ED_{50} 0.1 mg/kg *iv*) and enoxaparin (0.04 mg/kg *iv*) were required to reduce thrombosis in the venous thrombosis model, enoxaparin was more potent than rivaroxaban.

In a rabbit model of venous thrombus growth, oral rivaroxaban given non-prophylactically at a dose of 3.0 mg/kg, reduced thrombus growth to a similar extent as a rivaroxaban dose of 1.0 mg/kg *iv* and known efficacious doses of the control agents nadroparin and fondaparinux. In a murine thromboembolic death model, rivaroxaban provided effective protection with an ED_{50} of 0.3 mg/kg *iv*, and greater potency than enoxaparin (ED_{50} 7 mg/kg *iv*). In a rat model of tissue factor (TF)-induced hypercoagulability, rivaroxaban dose-dependently inhibited formation of thrombin-antithrombin (TAT), but low doses did not affect TAT generation. The direct thrombin inhibitor melagatran was also effective in inhibiting TAT generation at high dosages, but in contrast to rivaroxaban significantly increased TF-induced hypercoagulability at the lower doses.

Bleeding time models in rats and rabbits were used to evaluate the antihemostatic effect of rivaroxaban. Antithrombotic doses below the ED_{50} required for antithrombotic efficacy in the rat and rabbit AV-shunt models did not significantly affect bleeding times. At higher doses, bleeding times were prolonged in a dose-dependent manner. The ratio "antithrombotic activity/bleeding risk" of rivaroxaban was comparable to enoxaparin.

Rivaroxaban did not reduce the antithrombotic activity of enoxaparin and heparin in a rat AV-shunt model. Additive antithrombotic effect was observed after concomitant administration of rivaroxaban with either enoxaparin or heparin.

Rivaroxaban (0.1 and 0.3 mg/kg *iv*) was combined with anti-platelet drugs, acetylsalicylic acid (ASA, 3 and 10 mg/kg *po*) and clopidogrel (1 and 3 mg/kg *po*) separately or in a combination. Concomitant use of rivaroxaban and ASA, rivaroxaban and clopidogrel, or rivaroxaban, ASA and clopidogrel may have greater antithrombotic potency than the individual treatments, but an increased bleeding risk at higher clopidogrel doses has to be considered.

In general, the pharmacological testing demonstrated that rivaroxaban inhibits FXa, leading to secondary changes in coagulation parameters like aPTT and PT. Efficacy was shown in various thrombotic models and there appears to be a dose margin between the antithrombotic effect and the risk for increased bleeding. However, variation between (and within) different animal models makes it difficult to estimate how large this margin is.

- Secondary pharmacodynamics

Secondary pharmacodynamics was evaluated in an extended screening of radio-ligand binding assays and enzyme assays. No non-specific effect was observed in these assays, indicating selectivity of rivaroxaban for its target enzyme FXa.

Rivaroxaban has a structural similarity to the antibiotic linezolid, sharing the oxazolidinone structure. Oxazolidinones are clinically used as antibacterial agents due to their potential to inhibit bacterial protein synthesis. Since originally, no studies investigating potential inhibitory effects of rivaroxaban on bacterial protein synthesis were submitted, this was raised as a major point during the evaluation. Consequently, data from tests involving three Gram positive strains of bacteria were presented.

These data suggest that neither rivaroxaban, nor metabolites M1, M2 or M15 have any antibacterial activity at relevant concentrations. An additional, related concern is the possibility of mitochondrial toxicity caused by rivaroxaban. Linezolid is known to inhibit mitochondrial protein synthesis leading to an eventual depletion of mitochondrial-derived proteins and a loss of mitochondrial function. The apparent absence of the antibacterial effect of rivaroxaban (and its metabolites) does not necessarily imply an absence of an effect on mitochondria. Based on request in the same major point, additional data about the effect of rivaroxaban on mitochondrial protein synthesis were provided in form of a study on incorporation of [^{35}S]-L-methionine in isolated rat liver mitochondria. Although non-clincial studies cannot completely rule out a potential for mitochondrial toxicity of rivaroxaban the results of the *in vitro* study show that it might be low and thus it is not expected to be of concern for the currently approved short-term indication. However, any mitochondrial toxicity is of greater concern

for long-term treatment and exclusion of mitochondrial toxicity is particularly relevant in case an extension to long-term thrombotic prophylaxis is considered in the future. Therefore, in order to avoid the limitations of the *in vitro* study, the mitrochondrial toxicity of rivaroxaban will investigated in a non-clinical setting.

- Safety pharmacology programme

In safety pharmacology, the effects of rivaroxaban on vital organ systems (cardiovascular, respiratory and central nervous system) and other systems (hematology and blood coagulation, gastrointestinal function, renal function, and metabolism) were investigated in several *in vitro* and *in vivo* studies. The overall results showed no biologically relevant adverse effects on the central nervous, cardiovascular and respiratory system, renal function and metabolism, and gastrointestinal tract at the highest plasma levels achieved, which were 38-fold greater in rats and 31-fold greater in dogs than the therapeutic human plasma levels.

In studies addressing the risk for QT-prolongation in humans, no biologically relevant findings were observed in cardiovascular *in vitro* and *in vivo* studies. Thus, there appears to be no indication of a proarrhytmic potential of rivaroxaban.

In summary, the safety pharmacology studies did not suggest the likelihood of any acute adverse pharmacological effects of rivaroxaban, except bleeding. However, it should be noted that the safety pharmacology results were obtained after a single dose of rivaroxaban. The safety pharmacology programme was not designed to detect any long-term pharmacological effects. Some of the findings in the repeated dose toxicology studies may, at least partly, depend on pharmacological mechanisms.

- Pharmacodynamic drug interactions

Studies with co-administration of rivaroxaban with drugs showing anticoagulant or antiplatelet activity (acetylsalicylic acid, diclofenac, naproxen, warfarin, and clopidogrel) were performed to investigate the potential for clinical interactions and to provide the respective pre-clinical safety data. Single oral administration of rivaroxaban or the mentioned anticoagulants alone prolonged the tail transection bleeding time in rats in a dose-dependent manner. After co-administration of rivaroxaban with antihemostatic drugs, only additive effects on bleeding time were observed. The additive effects were most pronounced with naproxen and least prominent with diclofenac. Administration of activated charcoal together or shortly after dosing with rivaroxaban seemed to prevent or limit the absorption of rivaroxaban in rats.

The comprehensive set of non-clinical investigations characterises the potential for pharmacodynamic interactions between rivaroxaban and other antithrombotic drugs regarding antithrombotic efficacy and risk for bleeding. It appears that there might be therapeutic advantages with combined administration, particularly for a possible long-term use. Furthermore, some results indicate that the recombinant factor VII and factor VIII bypassing activity (FEIBA) might be useful antidotes in case of a rivaroxaban overdose. These assumptions must, however, be confirmed in clinical trials to establish their clinical relevance.

Pharmacokinetics

Non-clinical pharmacokinetic studies were conducted mainly in Wistar rats and dogs. Toxicokinetic data were collected from repeated dose studies in mice (CD-1), rats, dogs and female rabbits. General organ distribution was studied in Wistar rats and pigmented rats; placental transfer and excretion into milk was studied in female Wistar rats. Plasma protein binding and metabolism were investigated *in vitro* in several species, including Cynomolgus monkeys and humans. Several *in vitro* studies were conducted to characterise the involvement, inhibition and induction of cytochrome Ps (CYPs), P-gp and Bcrp. Finally, cell permeability was studied in Caco-2 cells.

Absorption after a single oral dose of rivaroxaban was rapid in both rats and dogs with maximal plasma concentration achieved in about 0.5 hours. The extent of absorption was somewhat lower in rats (67%) than in dogs (92%). After repeat dosing for 4 weeks, there was an increased absorption in rats, but not in mice or dogs. Higher exposure was observed in the female rats.

Protein binding varied between species, highest being in rat (98.7%) and lowest in rabbit (76.6%). Mechanistic studies showed that serum albumin is the main binding protein. However, a mechanistic study with human serum albumin (HSA) and oleic acid showed a striking difference in protein binding depending on the oleic acid concentration. This difference in protein binding is large enough to cover almost the entire range observed in different species.

Organ distribution after a single oral dose of rivaroxaban shows highest concentrations in the gastro-intestinal tract, liver and kidneys, lower concentrations in the brain. Rivaroxaban showed minor affinity to melanin-containing tissues, such as pigmented skin areas and eyes. After repeated oral administration to rats (14 consecutive daily administrations), radioactivity showed a moderate accumulation tendency. A slow elimination of rivaroxaban and its metabolites from bone after repeated dosing raised a suspicion of a potential connection with skeletal malformations observed in the reproductive toxicity studies. However, the detailed review of the data revealed that the absolute retention in bone is unlikely to prolong exposure and thus cause adverse effects on skeleton. Nevertheless, the embryotoxic observation (see section on Toxicology) remains and is addressed in the SPC. Volume of distribution was moderate, amounting to 0.3 L/kg for the rat and to 0.4 L/kg for the dog. Rivaroxaban was eliminated from rat and dog plasma with half-lives between 1 and 2 h. Rivaroxaban passes through the placental barrier but does not accumulate in the foetuses. In rats, the substance is excreted in milk.

Rivaroxaban is subject to oxidative metabolism in liver. The *in vivo* biotransformation pathways of rivaroxaban in man are similar to those in animals and are reflected in the *in vitro* investigation with liver microsomes and cultured hepatocytes from different species. The main metabolic pathway, the oxidative degradation of the morpholinone moiety, was catalyzed by CYP3A4/3A5 and CYP2J2 and lead *via* cleavage of the ring and further oxidation to the formation of metabolite M1. Another pathway is the hydrolysis of the amide bond, generating metabolites M15 and M13. Besides unchanged rivaroxaban, metabolite M1 was identified as main metabolite in the excreta of animals and man. Qualitatively, the animal metabolism of rivaroxaban is similar to that of man and there are no unique human metabolites. There are quantitative differences but none of them represent a cause for concern.

Elimination of rivaroxaban from plasma was rapid with no major circulating metabolites detected in plasma of rat, dog, and man. The main excretion routes in the investigated animal species and in man were renal and faecal/biliary. The rat differs from dogs and humans by a higher proportion of rivaroxaban and metabolites excreted in bile/faeces, and a lower proportion excreted in urine.

Toxicology

The toxicological and toxicokinetic profile of rivaroxaban has been characterized in a comprehensive non-clinical safety program, including studies to investigate the systemic toxicity as well as exaggerated pharmacodynamic effects after single and repeated administration, reproductive toxicity studies, genotoxicity studies as well as studies addressing specific questions, such as phototoxicity, toxicity of impurities, mechanistic studies.

To achieve sufficient exposure levels in animals a specific formulation was developed allowing a thorough characterization of the non-clinical safety profile of rivaroxaban. In the majority of pivotal repeat dose studies including the reproduction toxicity studies as well as in some of the dose-range finding investigations for the carcinogenicity studies rivaroxaban was administered using this specific formulation. Due to the specific manufacturing process of this formulation, it contains a significantly altered impurity spectrum. Hence, the batches used in these studies could not be considered as representative for drug substance and drug product. Therefore, a 4-week oral (gavage) toxicity study in rats was performed with selected batch of micro-crystalline rivaroxaban drug substance, specifically prepared to contain impurities relevant in rivaroxaban drug substance and drug product. Furthermore, representative batches of micro-crystalline drug substance were tested in *in vitro* genotoxicity studies.

- Single dose toxicity

The acute toxicity of rivaroxaban was tested in male and female rats when administered orally and in mice of both genders when administered orally and intravenously.
No mortality was noted up to the highest technically feasible dose. Following ***i.v.*** bolus administration, apparent acute and transient clinical signs of toxicity appeared at the only tested dose of 25 mg/kg. Rivaroxaban was classified as moderately toxic in mice after intravenous and moderately toxic in both species after oral administration. No major toxicity findings were noted in both species after oral administration.

- Repeat dose toxicity with toxicokinetics

Repeat peroral dose toxicity studies have been performed in mouse (4-13weeks), rat (4-13-26weeks) and in dog (4-13-52weeks) to support long term use in patients.

Target toxicity and organ toxicity findings examined in mice with the low tested dose were: the significant decrease in leukocyte count and toxicity of liver. Decreased leukocyte count was evident in all toxicity studies. In case of low doses of the clinical crystal formulation of micronized rivaroxaban, focal liver necrosis together with increased liver weight and decrease in liver protein levels, e.g. serum ASAT and ALAT, activities of ECOD/EROD/ALD/GLU-T, were determined already at lowest dose level. Mice appear to be a sensitive species with regards to liver toxicity.

In rat, no treatment related mortality was reported in the toxicity studies with orally administered rivaroxaban. In the 13 week study using clinical crystal formulation of rivaroxaban, different treatment related effects were determined from the lowest dose levels tested: increased urine output, periportal inflammatory infiltrates/megakaryocytes in liver, transient increase in ALT and in the biomarker of cell leakage LDH, decrease in glutamate dehydrogenase with highest activity in periacinar hepatocytes, decrease in heart weight, pancreatic acinar hypertrophy, unilateral optic nerve fiber degeneration, and poplietal lymph node pigmentation. Sporadic liver lesions indicating induced liver necrosis were noted in single animal at higher dose level.

In the studies using the specific formulation of rivaroxaban, the main treatment related effects were: increased amount of IgG and IgA and increased incidence of pancreatic lesions. At higher doses, urine crystals formation together with increased creatinine and urea content and increased incidence of ovary follicle cysts were noted in the 26 week study. Studies with the specific formulation also revealed that ALT increased transiently up to 1-3 month of treatment without any signs of liver lesions at autopsy, performed 2-3 months later. In addition, decrease in the absolute and relative heart weight was persistent. Myocardiopathy was noted in two female rats in the 26 week study and reduced heart weight in all studies conducted in rats, which was considered related to rivaroxaban.

The increased incidence of pancreatic lesions reported in male rats is of concern especially when considering the possible link with the treatment related functional effects of rivaroxaban on acinar pancreas observed in clinical trials, e.g. increased lipase and amylase levels. In addition, the exposure profile of the compound in animals is relevant to that in humans. The detailed review of the data available on adverse effects related to pancreas was submitted and their possible relationship to rivaroxaban cannot be excluded. This adverse reaction is appropriately reflected in the SPC.

Similarly, the SPC refers to the rivaroxaban related induction of the immunoglobulin levels. Although no apparent and consistent exposure related elevation can be claimed and the values did not generally differ from the presented historical controls, the data from rat studies clearly suggest an increased formation of immunoglobulins. In addition, the values fluctuated considerably (concurrent study mean controls varied greatly between 33-113% of historical mean with high SD% values). The overall increases were not restricted to one gender and consistent across studies. No evaluation of potential clinical safety impact has been provided.

In dog, the observed coagulation time (PT and/or PTT) suggested treatment resistance development. Consequently, bleeding related observations were greater at week 13 than at week 52. The crystal formulation of rivaroxaban was not administered to dogs; instead the specific formulation was used. Slight dose dependent increase in liver weight was seen in the 4 week study, with minimal periportal vacuolation and centrilobular fat, but not in the longer studies. Four male dogs of the 52 week study had minimal to slight cytoplasmic vacuoles and/or inclusions in the liver. Increased level of transaminase was detected at higher dose level in both studies. In the 52 week study, a tendency for an increased variability in heart weight was seen. Treatment-related increase in the incidence of small dense nuclei of collecting duct epithelial cells in kidney was reported in males in the 52 week study. Exaggerated pharmacological activity (inhibition of blood coagulation) lead to severe haemorrhages with secondary anaemia. However, no intrinsic organ specific toxicity of rivaroxaban was revealed up to the highest dose tested.

Although the non clinical safety data demonstrated that the drug was well tolerated in dogs, rats and mice, the persistent adverse effects on liver, including changes of hepatic enzyme and bilirubin levels and incidence of liver necrosis, occurring in the species tested, constituted a significant concern. Further examination and a comprehensive comparison of hepatic data from all repeat dose studies in all species was requested and provided. The finding of focal liver necrosis in orally treated mice is considered related to rivaroxaban treatment, whereas the findings in rats and dogs are more ambiguous. Thus, the concern about possible hepatic toxicity remains but the clinical relevance is uncertain. Further clinical evaluation and risk management is needed and additional non-clinical studies are considered unlikely to resolve the issue. Analysis of the clinical liver data showed that abnormalities of liver function test occurred with a comparable or lower incidence in rivaroxaban *vs* enoxaparin treated subjects and most of them occurred in the early phase after surgery. The elevations were transient and returned to normal in the majority of cases.

- Genotoxicity

A standard battery of *in vitro* and *in vivo* genotoxicity tests was conducted and revealed no evidence for a genotoxic risk to patients under treatment. It was tested negative for *in vitro* mutagenicity and *in vitro* and *in vivo* clastogenicity. The effects of induced dose-dependent cytotoxicity in the mammalian cells were considered within historical control range rather than treatment related.

- Carcinogenicity

Considering the anticipated short term therapeutic use, the negative results of the genotoxicity tests, no relevant tissue retention and no evidence for any pre-neoplastic findings in the repeat-dose toxicity studies, the justification for waiving carcinogenicity studies was accepted. However, carcinogenicity studies in rat and mouse to support future indications with chronic use are ongoing.

- Reproduction Toxicity

Reproductive toxicity studies have been performed in rat and rabbit using the specific formulation of rivaroxaban. Fertility was unaffected by treatment of male and female animals, there was not obvious

negative effect on pups when the product was administered to dams. Placenta changes, such as necrotic borders, increased placenta weight or engorged-necrotic-pale, were seen in rat at low doses and in rabbit from mid doses upwards.

Increased post-implantation loss was observed in both species and total resorption or abortion in rabbit. Adverse liver findings on foetal liver and spleen were observed in rat in form of dark coloured spots. Moreover, the target organs in foetus were skeleton, where significant incomplete progressed ossification-dysplasia and skeletal malformations were observed, and heart blood vessels, where artery position of rats and ventricular septum in rabbit were affected. Similarly, other related studies confirm these observations. Although no direct effect on male or female fertility was reported in the fertility and early embryonic development study in rat, a dose-dependent increase in post-implantation loss was observed already at the lowest dose. The increase was significant at the higher doses. These observations were made in the embryo-foetal development study in rabbits.

The issues of post-implantation loss and developmental toxicity in animals were initially thought to be well within the range of historical control data. Neither can the malformation effects be considered related to reduced foetal weight or only to doses close to maternally toxic levels, since no supporting data exist. Thus, the increase in common malformations seen in both species at clinically relevant exposure and affecting mainly skeleton, heart and vessels appear to be related to rivaroxaban's pharmacodynamic activity. Other antithrombotic medicinal products have not been associated with these effects. In addition, true placenta and teratogenic effects of rivaroxaban cannot be excluded. Pregnancy and breastfeeding during rivaroxaban administration have therefore been contraindicated. The relevant information on placental toxicity, embryofoetal toxicity and teratogenicity are included in the SPC. In addition, pregnancy cases are routinely followed up and the measures related pregnancy are included in the Risk Management Plan.

- Toxicokinetic data

Toxicokinetic data were collected from repeated dose studies in mice (CD-1) rats, dogs and female rabbits. General organ distribution was studied in Wistar rats and pigmented rats; placental transfer and excretion into milk was studied in female Wistar rats. Based on the data obtained, no relevant changes in exposure were observed between single and repeated dosing in mice, rats and dogs or between male and female mice and dogs.

Toxicokinetic evaluation showed that sufficient safety margins to humans were obtained in repeated dose toxicity studies and in reproduction toxicity studies.

- Local tolerance

Local tolerability of rivaroxaban was tested in dogs after intravenous/paravascular/intraarterial administration. It was concluded that the local tolerance of injected rivaroxaban was not different from saline, but due to the oral administration route to humans, these studies are not regarded as significant for the proposed clinical use.

- Other toxicity studies

Phototoxicity
Photosafety of rivaroxaban has been addressed an *in vitro* phototoxicity assay. The compound-related radioactivity was found to accumulate in skin but the parent drug showed minimal light absorption in the range 290 to 300 nm. Above 300 nm no light absorption was seen. Rivaroxaban was tested negative in a phototoxicity test in mammalian cell with or without irradiation.

Mechanistic studies
A mechanistic study was performed to further explore the nature of the crystals found in the urinary sediment of rats in the 26-week study at doses of 50 mg/kg and above (PH-33611). Male and female rats were treated over 34 days with 200 mg/kg rivaroxaban. After microscopic examination of urine samples collected at day 24 the same crystals were found. Rivaroxaban was identified in the sediment which suggests that the crystals consist of rivaroxaban. Since rivaroxaban is excreted in rats *via* urine

(8.1 % of total radioactivity), it is most likely that the maximum solubility in the highly concentrated rat urine was exceeded, resulting in precipitation of unchanged drug.

Studies on impurities
A 4 week systemic toxicity study in rats using a batch of micronized drug substance, specifically prepared to contain all relevant impurities of rivaroxaban drug substance and drug product was conducted. With exception of an increase in coagulation time (pharmacologically related effect), no treatment-related adverse effects were observed in rats up to the highest dose tested. Furthermore, representative batches of micro-crystalline drug substance tested in *in vitro* genotoxicity studies showed no genotoxic effects.

In the specific formulation of rivaroxaban, a formulation not used in the clinical settings, anilino-morpholinone, an impurity formed by degradation of rivaroxaban during the melting process was detected. To characterize the toxicological profile of anilino-morpholinone and to allow a clear distinction between potential anilino-morpholinone and rivaroxaban-related effects, a 4 week oral (gavage) toxicity study with anilino-morpholinone was conducted. Anilino-morpholinone was well tolerated by rats without any treatment-related adverse events when given over 4 weeks up to and including 40 mg/kg. In a Salmonella/microsome assay anilino-morpholinone showed mutagenic effects. The impurities present in drug substance and drug product can be considered as qualified according to ICH Q3A guideline.

Ecotoxicity/environmental risk assessment

A phase I environmental risk assessment has been submitted for rivaroxaban. There is no need for a phase II assessment for the planned use of rivaroxaban.

2.4 Clinical aspects

Introduction

This is a complete application for approval of a new direct factor Xa inhibitor for oral use, Xarelto, 10 mg film-coated tablets, which contain the active substance rivaroxaban. The development programme for rivaroxaban was extensive and included a large number of clinical trials. The active treatment with rivaroxaban was administered to more than 1000 subjects enrolled in phase I studies, more than 2000 in phase II and more than 4500 in phase III. Amongst these were subjects belonging to special populations, such as patients with mild, moderate, or severe renal impairment, or mild or moderate hepatic impairment (classified as Child Pugh A and B).

In summary, the clinical investigations included single and multiple dose ascending studies to assess basic pharmacokinetic and pharmacodynamic characteristics of rivaroxaban and its metabolites, studies in special populations to evaluate the effects of intrinsic factors on pharmacokinetic and pharmacodynamic properties, as well as the drug-drug interaction studies guided by relevant pre-clinical information.

Patients in the phase II studies were administered rivaroxaban per os in various doses and safety, tolerability and efficacy of this treatment were compared to that of subcutaneously administered enoxaparin. The phase III programme included 3 major trials with patients with total knee or hip replacement examining safety and efficacy of orally administered rivaroxaban.

The claimed indication for Xarelto is:

Prevention of venous thromboembolism (VTE) in patients undergoing major orthopaedic surgery of the lower limbs.

The approved indication for Xarelto is:

Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery.

Formal scientific recommendations were given by the National Competent Authorities of France, UK, Spain, Germany and Sweden. The applicant received Scientific Advice from the CHMP in the sought indication in July 2003 and in September 2005. Amongst the major discussion topics were: choice of a diagnostic method for vein thrombosis, design of the dose confirmatory phase II trials, population selection in phase II trials, choice of the comparator, selection and definition of primary endpoints, characterisation and classification of bleeding events and others. The CHMP gave Scientific Advise also for different indications, as requested by the company.

During the clinical development programme the recommendations provided in relevant CHMP guideline within the therapeutic area: "Guideline on Clinical Investigation of Medicinal Products for Prophylaxis of High Intra- and Post-operative Venous Thromboembolic Risk" (CPMP/EWP/707/98) were followed.

There is no paediatric investigation plan. According to the European legislation valid at the time of the submission, there was no requirement to submit a paediatric investigation plan before July 2008.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant. The CHMP requested a routine GCP-inspection at the sponsor site and at two investigator sites in Colombia and Peru. Based on this inspection, the general performance of the sponsor can be considered as GCP compliant and the data reported by the sponsor for the Regulation of Coagulation in Orthopedic Surgery to prevent DVT and PE (RECORD) 2 study were deemed valid and reliable and can be used in the assessment of this marketing authorisation application.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

Pharmacokinetics

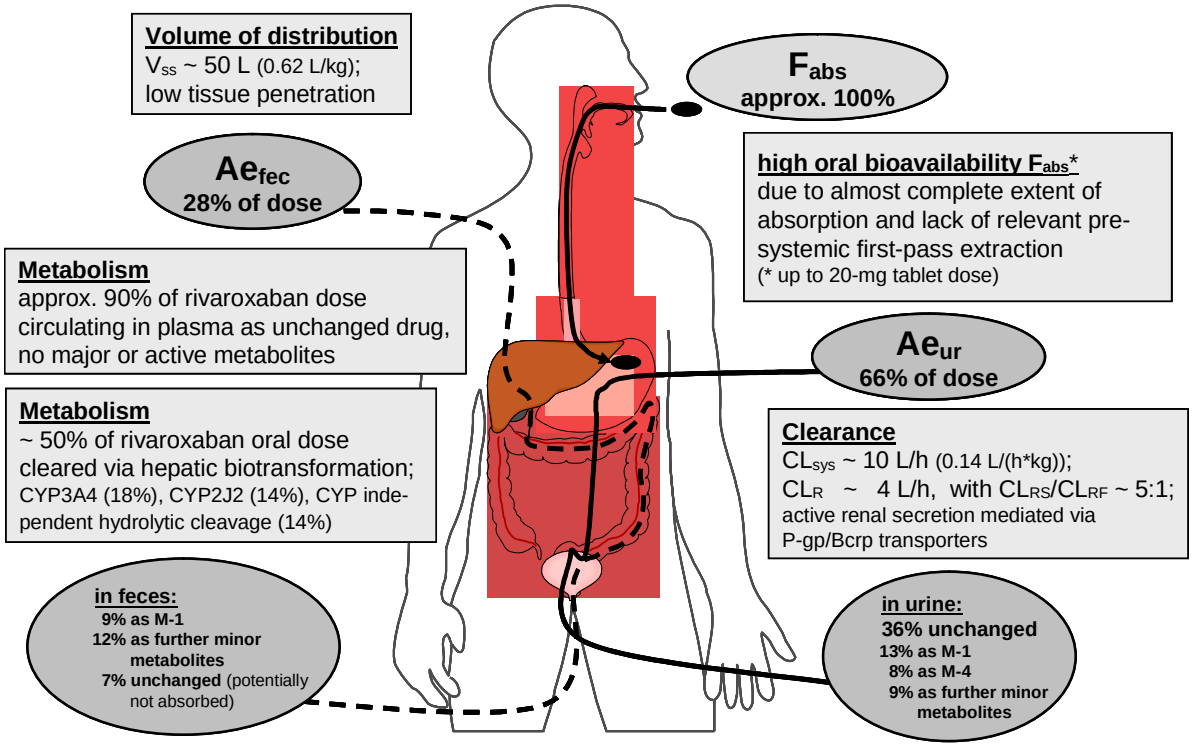
Pharmacokinetic profile of rivaroxaban was evaluated in the phase I programme and additional data were also obtained from patients in three phase II studies. Plasma rivaroxaban concentrations were measured using a validated high-performance liquid chromatography assay with tandem mass spectrometric detection (HPLC-MS/MS method). Rivaroxaban concentration in urine was measured using a validated HPLC assay with UV detection. Pharmacokinetic parameters in phase I studies were generally calculated by non-compartmental methods. Nonlinear mixed effects modelling (population pharmacokinetic analysis) was used to evaluate pharmacokinetics in patients . The pharmacokinetic studies included single, multiple dose trials, examinations of metabolism and excretion patterns, effects of age, gender, weight, race, renal and hepatic impairment and concomitant medication on the pharmacokinetic profile of the drug.

In addition, in vitro pharmacokinetic investigations pertinent to pharmacokinetics using human biomaterials such as hepatocytes microsomes, recombinant CYP isoforms, human plasma, Caco-2 cells and others, have been conducted in support of characterisation of rivaroxaban pharmacokinetic profile.

The composition of the tablet formulation used in the phase III programme for VTE prevention following major orthopaedic surgery is identical with the intended commercial formulation and remained unchanged when compared to the phase I/II formulation studies, except the colour of the film-coat.

An overall description of rivaroxaban pharmacokinetics is displayed in the following figure.

Summary of rivaroxaban mass balance, excretion pattern, distribution and clearance properties in man



Ae_{ur}	amount excreted into urine
Ae_{fec}	amount excreted into bile/feces
Bcrp	breast cancer resistance protein
CL_{sys}	systemic (plasma) clearance
CL_R	renal clearance (via active secretion CL_{RS} and glomerular filtration CL_{RF})
CYP3A4	cytochrome P450 3A4
CYP2J2	cytochrome P450 2J2
F_{abs}	absolute bioavailability
M-1, M-4	metabolites M-1 and M-4
P-gp	P-glycoprotein
V_{ss}	volume of distribution at steady-state

all numbers are approximate; sum of percentages is 94% (= recovery in human mass balance study)

- Absorption

Following the oral administration of 5-10 mg solution of rivaroxaban, the absorption is rapid with Cmax reached after approximately 30 min. Upon administration of rivaroxaban tablet, a flatter profile was observed with mean peak concentrations occurring after 2-4 h. Rivaroxaban terminal half-life increases with dose and this suggests absorption limited elimination. *In vitro* data from a Caco-2 cell assay indicates intermediate permeability.

Food (a high-fat, high-calorie meal) did not affect the area under plasma concentration vs time curve (AUC) and Cmax for the final 10 mg tablet, but absorption was delayed in the fed state showing a lag-time of approximately 0.5 h and a delay in median tmax of about 0.5 h. The F_{abs} was not determined for the 10 mg tablet, but was complete for 5 mg and around 66% for 20 mg dose in a fasting state. Based on this, on the dose-proportional exposure observed between 5 and 10 mg and the lack of food effect for the 10 mg final formulation, the bioavailability of the 10 mg tablet seems to be 100% in healthy volunteers. However, a reduced bioavailability with increased dose was included in all population PK models of phase II data. The bioavailability seems to be about 80% at the 10 mg dose in patients. Rivaroxaban tablets were administered in the pivotal phase III trials irrespective of food intake and the final formulation was used in phase III studies, thus omitting the need for bioequivalence studies.

- Distribution

Plasma protein binding for rivaroxaban in humans is high, approximately 92% to 95% *in vitro*, with serum albumin being the main binding component. No concentration-dependency of total plasma concentration up to 3100 µg/L rivaroxaban (approximately 20-fold the maximum therapeutic concentration) was observed. Due to its high plasma protein binding rivaroxaban is not expected to be dialyzable. The binding of rivaroxaban to plasma proteins is fully reversible. The human plasma-to-blood partition coefficient is 1.40. The volume of distribution at steady-state (Vss) is approximately 50 L (0.62 L/kg), indicating a low affinity to tissues, which is in agreement with he observed data in animals.

Rivaroxaban has been characterised *in vitro* as a substrate for the active transport proteins P-glycoprotein (P-gp) and BCRP ('breast cancer resistance protein').

- Metabolism and elimination

Rivaroxaban is eliminated via three major routes. Approximately 36% of the dose is excreted via kidney in form of the unchanged drug, involving the active transporter-mediated secretion by P-gp and BCRP. Further approximately 14% of the dose is eliminated via hydrolysis of the amide bonds and approximately 32% of the dose is eliminated via oxidative metabolic pathways. The CYP3A4 and CYP3A5 isoforms are responsible for metabolizing around 18% and CYP2J2 around 14% of the dose.

After intravenous administration of rivaroxaban, the mean systemic clearance was 10.7 l/h. The renal clearance was 4.7 l/h, with the major part mediated by active secretion. Mean terminal elimination half-live of rivaroxaban after intravenous administration was 4.5 h. After the oral administration of 10 mg dose, elimination becomes absorption rate limited with terminal half-life of on average 7 to 11 hours.

In vitro metabolism of rivaroxaban was evaluated in liver microsomes and hepatocytes identifying 18 metabolites. After oral administration of [^{14}C]rivaroxaban 10 mg oral solution to humans, 66% of the dose was recovered in urine and 28% in faeces. In total, 89% of the dose administered could be attributed to known structures. Unchanged drug was the main compound in plasma at all investigated time-points and accounted for 89% of the $AUC_{(0\text{-}tn)}$ of total radioactivity. No major or active circulating metabolites were detected in plasma and the main metabolite in plasma, M1, accounted for about 3% of plasma radioactivity.

Approximately 36 % of the dose was excreted unchanged in urine. Metabolites M1 and M4 were detected in urine as the major metabolites and accounted for around 13 % and 8 % of the dose, respectively. The main constituents in human faecal extracts were the unchanged drug (7 % of the dose) and the M1 metabolite (9 % of the dose). Urine and faeces excretion of M7 accounted for 6.6% of the dose. Other metabolites, M2, M5, M6, M8 and M9 each constituted less that 4% of the administered dose.

There is no indication of a potential metabolic interconversion of S- to R-rivaroxaban in humans.

- Dose proportionality and time dependencies

Rivaroxaban displays a dose dependent pharmacokinetics with less than proportional increase in the AUC as the dose is increases. The non-linearity becomes evident in the fasting state at doses above 15 mg. However, the pharmacokinetics seems to be fairly proportional up to 30 mg in Caucasian volunteers and to 20 mg in Japanese and Chinese volunteers in the fed state. Overall, in the lower dose range including the 10 mg dose, no major deviation from linearity for rivaroxaban was observed. However, at higher doses a less than proportional increase in exposure can be expected. A ceiling effect with no additional increase in exposure with increased dose is reached around 50 mg dose, even if taken with food by healthy elderly subjects.

- Variability

Variability in pharmacokinetics is moderate with inter-individual variability (expressed as coefficient of variation) ranging from 18 to 33% for AUC, and from 16 to 39% for Cmax in Phase I studies. Intra-individual variability was reported to be on average (expressed as median) 14% for AUC, and 19% for Cmax. In the PK analyses from population in the phase II studies, inter-individual variability in clearance of 34-38% was observed at steady state (3-5 days after the operation) but was considerably higher on the first day after the operation, about 70%.

- Special populations

Pharmacokinetics in special populations were evaluated in specific phase I studies in subjects with mild to severe renal impairment, mild to moderate hepatic impairment, elderly, subjects with high or low weight. In addition, differences between gender and different race were evaluated in phase I studies.

Gender, race and weight have none or only a small effect on rivaroxaban AUC. The drug exposure is increased in elderly, in patients with renal impairment and in patients with hepatic impairment (patients with cirrhosis classified as Child Pugh A or B). In addition, patients with renal and hepatic impairment are more sensitive to rivaroxaban and have a steeper PK/PD relationship resulting in a larger increase in PD effects than in PK effects.

Elderly had a 40-50% higher AUC. In subjects with mild, moderate and severe renal impairment rivaroxavan AUC increased by 44%, 52% and 64%, respectively, while the AUC of factor Xa increased by 50, 86 and 100% and AUC of PT increased by 33, 116 and 144%, respectively, compared to subjects with normal renal function. The group of patients with severe renal impairment included subjects with creatinine clearance 15-30 ml/min. A higher exposure and increase in factor Xa could be expected in patients with creatinine clearance <15 ml/min. Rivaroxaban AUC was increased by 15% in patients with mild hepatic impairment (Child Pugh A) and by 127% in those with moderate hepatic impairment (Child Pugh B). The corresponding increase in unbound exposure was 157% in moderate hepatic impairment. The AUC for Factor Xa was increased 2.6-fold and for PT 2.1 fold in subjects with moderate hepatic impairment. A PK/PD analysis between rivaroxaban concentration and PT using a “close-to-linear” model indicated a steeper slope in patients with reduced renal or hepatic function.

Thus, safety in patients with renal and/or hepatic impairment was a subject of discussion as a result of which, the SPC has been revised. In summary, the SPC proposes caution in patients with severe renal impairment (creatinine clearance 15-30 ml/min); the use in patients with creatinine clearance <15 ml/min is not recommended. Furthermore, a contraindication is captured in the SPC for rivaroxaban in patients with hepatic disease, which is associated with coagulopathy and clinically relevant bleeding risk. Caution is advised for cirrhotic patients with moderate hepatic impairment (Child Pugh B). Patients at increased risk for bleeding are to be monitored.

- Pharmacokinetic interaction studies

The *in vitro* non clinical studies showed a low potential for rivaroxaban to inhibit CYP450 isoenzymes, P-gp and BCRP. This was confirmed *in vivo* in interaction studies with midazolam (CYP3A4 substrate), atorvastatin (CYP3A4 and Pgp substrate), warfarin (CYP2C9 substrate) and digoxin (Pgp substrate).

In vivo interaction studies are summarised in Table 1. To quantify the extent of interactions, *in vivo* drug-drug interaction studies were conducted within the clinical study program with ketoconazole (strong CYP3A4 and P-gp inhibitor), ritonavir (strong CYP3A4 and P-gp inhibitor), erythromycin (moderate CYP3A4 and P-gp inhibitor), clarithromycin (strong CYP3A4 inhibitor and moderate P-gp inhibitor) and rifampicin (potent inducer of CYP3A4). The results of the *in vivo* interaction studies show that rivaroxaban exposure is increased by inhibitors of CYP3A4, P-gp and BCRP, and is decreased by CYP3A4 inducers. Doubling of rivaroxaban AUC was observed when co-administered with ketoconazol and ritonavir, while rivaroxaban AUC increased by 50% with clarithromycin and by

30% with erythromycin. Modelling studies with ketoconazole and ritonavir suggest that ketoconazole inhibits rivaroxaban hepatic clearance almost completely and also has a moderate effect on its renal secretion, while ritonavir strongly inhibits renal secretion and largely affects the hepatic clearance. Furthermore, based on the modelling study results, the moderate CYP3A4 inhibitor erythromycin inhibits hepatic clearance by 30%, but it does not affect renal secretion. It is of note that observed effects of ritonavir and ketoconazole represent a worst case scenario with inhibition of both, the CYP-mediated metabolism and the renal secretion. Strong inhibition of either cytochrome-mediated metabolism or renal secretion is expected to result in lower effects than that observed with ketoconazole and ritonavir together. Nevertheless, the SPC was amended appropriately to reflect the fact that the co-administration of rivaroxaban with potent inhibitors of CYP3A4 and/or P-gp, such as ketoconazole or ritonavir, may lead to an increase in rivaroxaban AUC and Cmax, and moreover to a more pronounced pharmacodynamic effects along with an increased risk of bleeding. The use of rivaroxaban is not recommended in patients receiving concomitant systemic treatment with the azole-antimycotics or HIV protease inhibitors. Fluconazol is expected to have a smaller effect on rivaroxaban exposure and can be co-administered with caution. The effects observed with clarithromycin and erythromycin were not considered clinically relevant.

The data from phase III studies indicate lower efficacy of rivaroxaban in patients with concomitant CYP3A4 inducers. The AUC of rivaroxaban decreases by 50% when used concomitantly with CYP3A4 inducer rifampicin. Hence, it cannot be excluded that other inducers may have a similar clinically relevant effect on rivaroxaban. The SPC recommends that the co-administration of CYP3A4 inducers and rivaroxaban should be made with caution.

Two specific interaction studies were conducted to investigate the influence of antacids and H2-receptor antagonists, on the absorption and oral bioavailability of rivaroxaban given as 30 mg tablets. Neither ranitidine nor antazide had any relevant impact on pharmacokinetic or pharmacodynamic properties of rivaroxaban.

Summary of Rivaroxaban interaction studies. Geometric Mean Ratios [90% Confidence Intervals (CI)], (range) or [95% prediction interval (PI)]

Influence of	Rivaroxaban AUC ratio [90% CI] *(range)* or *[95% PI]*	Rivaroxaban C_{max} ratio [90% CI] *(range) or [95% PI]*	Effect on other drug ratio [90% CI] *(range)*
High-fat, high-calorie meal			
• 10-mg IR tablet	0.99 [0.93 – 1.05]	1.03 [0.94 – 1.14]	
Change in gastric pH, n=12			
• Ranitidine 150 mg bid for 3 d • Rivaroxaban 30 mg sd, fasting	1.01 [0.85 – 1.20] *(0.46-1.86)*	1.08 [0.77 – 1.50] *(0.41-3.0)*	
Adsorption/change in gastric pH			
• Antacid , n=11 • Rivaroxaban 30 mg sd, fasting	0.95 [0.83 – 1.08] *(0.74-1.66)*	0.87 [0.73 – 1.03] *(0.54-1.69)*	
CYP 3A4 substrate			AUC:
• Midazolam 7.5 mg single dose • Rivaroxaban 20 mg sd, n=12	1.01 [0.92 – 1.12] *(0.65-1.56)*	0.88 [0.72 – 1.07] *(0.42-1.76)*	0.89 [0.75-1.05] *(0.61-1.64)*
CYP 3A4 / P-gp substrate			AUC:
• Atorvastatin • Rivaroxaban 20 mg, n=19	0.99 [0.91-1.08] *(0.70-1.46)*	0.98 [0.89-1.07] *(0.56-1.37)*	1.0 [0.93-1.09] *(0.70-1.95)*
P-gp substrate			AUC:
• Digoxin 0.375 mg qd, n=20 • Rivaroxaban 20 mg bid for 9 d	0.90 [0.83 – 0.97]	1.0 [0.85 – 1.14]	1.08 [0.97-1.20]
CYP 3A4 / P-gp inhibitor (weak-to-moderate) • Erythromycin 500 mg tid 4d • Rivaroxaban 10 mg sd, n=12	1.34 [1.23 – 1.46] *[1.1 – 1.7]*	1.34 [1.21 – 1.48] *[1.0 – 1.8]*	
CYP 3A4 / P-gp inhibitor (moderate) • Clarithromycin 500 mg bid 5d • Rivaroxaban 10 mg sd, n=15	1.54 [1.44 – 1.65] *[1.27 – 1.89]*	1.40 [1.30 – 1.52] *[1.12 – 1.76]*	
CYP 3A4 / P-gp inhibitor (strong)			
• Ketoconazole 200 mg 4d n=12	1.82 [1.59 – 2.08] *[1.28 – 2.58]*	1.53 [1.27 – 1.85] *[0.92 – 2.53]*	
• Ketoconazole 400 mg 5d n=20	2.58 [2.36 – 2.82] *[1.71 – 3.89]*	1.72 [1.61 – 1.83] *[1.29 – 2.28]*	
• Ritonavir 600 mg 5d, n=12 • Rivaroxaban 10 mg	2.53 [2.34 – 2.74] *[1.92 – 3.35]*	1.55 [1.41 – 1.69] *[1.12 – 2.15]*	
CYP 3A4 / P-gp inducer (strong)			
• Rifampicin 150-600 mg 6d • Rivaroxaban 20 mg sd, n=18	0.51 [0.48 – 0.55] *[0.38 - 0.69]*	0.78 [0.70 – 0.87] *[0.48 - 1.27]*	

sd: single dose, d: days

Combination of risk factors

Patients with moderate renal and hepatic impairment or with moderate renal or hepatic impairment and concomitant administration of inhibitors of CYP3A4, P-gp and/or BCRP could have a very large increase in rivaroxaban exposure and increased bleeding risk. The SPC includes a warning in patients

with moderate renal impairment and co-administration with other drugs increasing rivaroxaban exposure.

Pharmacodynamics

- Mechanism of action

Rivaroxaban is a competitive, selective, and a direct inhibitor of serine protease coagulation factor Xa (FXa). The activated FXa plays a central role in the cascade of blood coagulation. It is activated by both the intrinsic and extrinsic coagulation pathways. FXa directly converts prothrombin to thrombin through the prothrombinase complex, and ultimately, this reaction leads to fibrin clot formation and activation of platelets by thrombin.

- Primary and Secondary pharmacology

The pharmacodynamic investigations provided evidence of a dose dependent inhibition of FXa induced by rivaroxaban. The PT and aPTT were prolonged dose dependently, thus showing the anti-coagulatory effect induced by rivaroxaban. The correlation between concentration and effect was well pronounced for the PT, followed by the aPTT. Rivaroxaban had no effect on thrombin content in plasma and did not interact with antithrombin. This is in accordance with the normal activity profile of a direct FXa inhibitor.

Furthermore, thrombin generation was investigated both at a surface and a tissue factor induced activation of the coagulation system. A significant reduction of thrombin generation by rivaroxaban in doses proposed for clinical use has been observed.

The pharmacodynamic and pharmacokinetic relationship between rivaroxaban concentration and several endpoints, such as FXa inhibition, PT, aPTT and Heptest, has been thoroughly evaluated. The relationship between rivaroxaban concentration and FXa activity was described by an E_{max} model. In the different studies EC_{50} ranged between 200 and 300 µg/l and E_{max} approached complete inhibition. The baseline PT was influenced by the surgery in the patients and a time-dependent baseline was incorporated in the model. A difference in the concentration-PT slope at post-surgery and at steady state was identified. It was assumed that the linear PT model supports the use of PT as exposure marker in phase III trials for rivaroxaban concentrations up to 800 µg/l. Although the PT may be used as a marker for rivaroxaban exposure, the time dependent baseline in PT post-surgery and the difference in concentration-PT slope for different measurements indicate difficulties in using PT as exposure marker during the first days after surgery before steady state conditions have been reached. It is important to use the same method for all PT measurements.

An exploratory evaluation of the relation between PT and bleedings in phase III studies was conducted but PT threshold predictive of bleedings was not identified. Similar analysis for phase II data was also provided. The bleeding risk does increase with dose, but the dose-bleeding event relationship appears to be shallow. Neither PK parameters (AUC, C_{max} or C_{min}) nor PT can be used as indicator of bleeding risk due to the shallow concentration-response and overlapping concentrations/PT in patients with and without bleeding events in the studied dose range in the studied population. The relationship between Factor Xa and bleedings has not been evaluated, but is not expected to differ from that observed for PT and the different PK parameters. No specific PK/PD evaluation for clinical outcome (prevention of VTE) has been conducted.

There is a need to develop a laboratory test for detecting increased exposure or pharmacodynamic activity. The Applicant has, as a follow-up measure, undertaken to validate modified commercially available tests for estimations of the pharmacodynamic activity of rivaroxaban that could be used in routine clinical setting. Information on expected range of such a variable or corresponding rivaroxaban concentration after administration of rivaroxaban 10 mg q.d. could potentially be used in monitoring risk patients, and be used in dose adaptation, if needed. Information regarding range of PT (Neoplastin) at 2-4 h after dose at steady state (5th/95th percentiles ranged from 13 to 25 sec) and at baseline (mean 13 s 5th/95th percentiles ranged from 12 to 15 sec) is included in section 5.1 of the SPC, and can serve as a rough guide until a better laboratory test is available.

Although it may not be possible to identify the exact cut-off for hemorrhagic risk, for doses above 20 mg o.d. or conditions, which lead to an exposure equivalent to doses above rivaroxaban 20 mg o.d., monitoring of subjects for signs of bleeding complications after initiation of treatment is warranted. This issue is addressed in the SPC. This may be done by regular physical examination of the subjects, close observation of the surgical wound drainage and periodic measurements of haemoglobin.

Although the non clinical investigations did not identify a QTc prolonging activity of rivaroxaban in hERG channel or Purkinje fibres experiments or in anesthetized dogs, a comprehensive study examining the potential for this effect was performed in accordance with the ICH E14 guidance. The results of this study in healthy volunteers did not indicate that rivaroxaban would induce a clinically relevant QTc prolongation.

Pharmacodynamic interaction studies have been performed with rivaroxaban and different agents with anti-haemostatic properties (e.g. enoxaparin, aspirin, naproxen, clopidogrel). The results from these studies did not reveal any unexpected pharmacodynamic interactions. Co-administration of enoxaparin with rivaroxaban resulted in an additive pharmacodynamic effect, as measured by anti-FXa assay. The effect of bleeding time prolongation during the co-administration of clopidogrel seems to be more pronounced. The present warning in the SPC concerning other medicinal products affecting haemostasis therefore seemed to be sufficient in the orthopaedic patients, who are currently treated with rivaroxaban. The use of low doses of rivaroxaban and warfarin confirmed that no over-additive effects were observed at the doses investigated and this forms the basis for further planning of confirmatory investigations.

From a clinical point of view, the primary and secondary pharmacodynamic effects were considered to be sufficiently characterised.

Clinical efficacy

- Dose response study(ies)

Overall, three dose-ranging studies aimed do explore the dose range of rivaroxaban from 2.5 to 30 mg bid and one study was conducted with a dose range from 5 to 40 mg od. All trials evaluated rivaroxaban treatment for 8-10 days in comparison with enoxaparin 40 mg od *sc* or 30 mg twice. Except for study 10942 (phase IIa) all phase IIb studies were performed as randomized, adequately controlled, double-blind studies in the target population at high risk for VTE. They had the same primary efficacy composite endpoint (any DVT and non fatal PE and death from all causes) and efficacy was measured with bilateral venography. This is in accordance with the CHMP recommendations. While three dose finding studies were performed in elective hip replacement surgery (10942, 10944 and 11527), dose finding in knee replacement surgery was done only in one study (10945). Studies included in the phase II program were adequately designed and in accordance with the current recommendations made by the CHMP concerning the study design of such studies in the guideline on clinical investigations of drugs for prophylaxis of intra- and post-operative venous thrombotic risk (2000).

Overview of the dose-ranging studies

Study	population	N (PP-pop)	Dose arms, mg.
10942	Hip replacement	466	2.5 bid, 5 bid, 10 bid, 30 od, 20 bid, 30 bid
10944	Hip replacement	548	2.5 bid, 5 bid, 10 bid, 20 bid, 30 bid
10945	Knee replacement	366	2.5 bid, 5 bid, 10 bid, 20 bid, 30 bid
11527	Hip replacement	618	5 od, 10 od, 20 od, 30 od, 40 od

The major phase II efficacy and safety results, as compiled from these 4 studies and by total daily doses are summarised below:

Incidence rates (%) for the primary efficacy endpoint and bleedings by total daily doses (tdd), phase II studies

Study	Rivaroxaban, tdd						Enoxaparin
	5 mg	10 mg	20 mg	30mg	40 mg	60 mg	40x1 or 30x2
Efficacy							
10942	22	24	20	15	10	17	17
10944	15	14	12	na	18	7	17
10945	32	40	23	na	35	25	44
11527	15	11	9	14	6	na	25
Safety, any major bleeding event							
10942	1.3	2.5	7.4	4.5	6.5	12.2	0.0
10944	0.8	2.2	2.3	na	4.5	5.4	1.5
10945	1.0	0.0	1.9	na	4.1	7.5	1.9
11527	2.3	0.7	5.0	4.9	5.8	na	1.9
Any bleeding event							
10942	11.8	11.3	19.1	21.6	19.5	24.3	7.4
10944	5.3	11.0	12.8	na	18.7	10.8	6.1
10945	8.0	7.8	6.8	na	20.4	21.7	8.7
11527	7.8	6.3	10.1	13.4	19.0	na	8.9

The efficacy primary endpoint was almost entirely driven by asymptomatic DVT. No clear dose-efficacy response relationship could be established. However, the relationship can be regarded as unexpectedly flat and the lowest dose seem to be associated with VTE incidence rates comparable to, or even lower than those associated with the standard enoxaparin regimen. It is not unreasonable to assume that these might be highly effective dose regimens and more pronounced effect cannot be gained by intensified anticoagulation. It may well be that already the 5 mg dose of rivaroxaban provides a nearly maximal clinical effect that is achievable by the type of pharmacological effect exerted by rivaroxaban in this patient group. The flat dose relationship may give rise to some concerns related to a possible uncertainty about the true effects in modern orthopaedic treatment. It is, however, considered unethical to request placebo-controlled trials in this therapeutic area.

The incidence of bleedings seems to be clearly related to the dose differences. The higher bleeding rates associated with 10 mg rivaroxaban treatment in studies 10942 and 10944 as compared to the enoxaparin regimen may be of some concern but the absolute figures are low. In addition, the design of study 10942 was open labelled, which might bring bias in reporting rates. The conclusion that 10 mg od seems more favourable than 5 mg bd from a safety perspective does not appear very robust based on these data. On the other hand, the 5 mg bid regimen does not appear to carry any obvious advantages and 10 mg od is expected to be associated with better compliance in clinical practice. Therefore, the compiled data on effect and safety of the product indicate that the choice of 10 mg od does not seem unreasonable.

With regard to efficacy, all four studies demonstrated good evidence for lower event rates and lower incidence rates for the primary efficacy endpoint for all rivaroxaban treatment groups compared to enoxaparin.

- Main studies

The clinical efficacy of rivaroxaban in the prevention of venous thromboembolism (VTE) in patients undergoing major orthopedic surgery of the lower limbs was investigated in 3 randomized, double-blind phase III trials *vs* enoxaparin: Study 11354 (RECORD 1), Study 11357 (RECORD 2) in hip replacement surgery and Study 11356 (RECORD 3) in patients undergoing knee replacement surgery.
In the studies RECORD 1 and RECORD 3, the treatment duration is essentially the same in the two treatment groups compared within the studies. However, RECORD 2 compares two groups that differ both, with regard to the prophylactic agents as well as to the treatment duration. Thus, it may in this study be partly difficult to evaluate to what extent any differences in efficacy or safety results are related to the study drugs or to the duration of treatment and this trial is considered supportive to the main RECORD 1 and RECORD 3 studies.

Overview of pivotal phase III efficacy studies[a]

Study number/ type of surgery	Design	Rivaroxaban dose (mg) and treatment duration	Enoxaparin dose (mg) and treatment duration	Number of subjects exposed to rivaroxaban	Number of subjects exposed to enoxaparin
RECORD 1: Regulation of Coagulation in Orthopedic Surgery to prevent DVT and PE, controlled, double-blind, randomized study of BAY 59-7939 in the extended prevention of VTE in patients undergoing elective total hip replacement					
11354 (RECORD 1) THR	randomized, double-blind, double-dummy parallel-group	10 od 35 ± 4 days	40 od 36 ± 4 days	2266 R 2209 VFS 1595 MITT	2275 R 2224 VFS 1558 MITT
RECORD 2: Regulation of Coagulation in Orthopedic Surgery to Prevent DVT and PE, Controlled, Double-Blind, Randomized Study of BAY59-7939 in the Extended Prevention of VTE in Patients Undergoing Elective Total Hip Replacement.					
11357 (RECORD 2) THR	randomized, double-blind, double-dummy parallel-group	10 od 35 ± 4 days	40 od 13 ± 2 days	1252 R 1228 VFS 864 MITT	1257 R 1229 VFS 869 MITT
RECORD 3: Regulation of Coagulation in Orthopedic Surgery to Prevent DVT and PE; a controlled, double-blind, randomized study of BAY 59-7939 in the prevention of VTE in subjects undergoing elective total knee replacement					
11356 (RECORD 3) TKR	randomized, double-blind, double-dummy parallel-group	10 od 12 ± 2 days	40 od 13 ± 2 days	1254 R 1220 VFS 824 MITT	1277 R 1239 VFS 878 MITT

Abbreviations: od=once daily; MITT=modified intent-to-treat analysis; R=randomized; THR=total hip replacement; TKR=total knee replacement; VFS=valid for safety analysis;
[a] In all studies, the first dose of rivaroxaban was to be administered 6 to 8 h postoperatively, whereas the first dose of enoxaparin was to be administered preoperatively.

METHODS

Study Participants
Men and women aged ≥18 years scheduled for elective total hip replacement (RECORD 2) or elective total knee replacement (RECORD 3) were eligible for the studies.

Among the exclusion criteria the following were of major importance:
- Active bleeding or high risk of bleeding contraindicating treatment with low- molecular-weight heparin.
- Significant liver disease (e.g. acute clinical hepatitis, chronic active hepatitis, cirrhosis).
- Contraindication listed in the labelling or conditions precluding subject treatment with enoxaparin requiring dose adjustment (e.g. severe renal impairment and conditions in the national label of enoxaparin).
- Pregnant and breast-feeding women and women with child-bearing potential not using adequate birth control method.
- Patients with drug or alcohol abuse.
- Ongoing oral anticoagulant therapy that could not be stopped in the opinion of the investigator.

Overall, a wide population of patients undergoing hip or knee replacement were eligible according to the inclusion criteria. There were not many exclusion criteria, which is thought to be advantageous. Hip fracture patients were not included and this is important to consider in relation to the wording of the indication as there is a lack of experience in this patient subgroup.

Treatments
The 3 pivotal phase III studies used different regimens for investigation VTE prevention: in major orthopaedic surgery:

- Extended prevention of VTE in Study 11354 (RECORD 1) (total hip replacement (THR) 5-week administration of rivaroxaban and enoxaparin)
- Extended *vs* short-term prevention of VTE in Study 11357 (RECORD 2) (THR, 5-week administration of rivaroxaban; 2-week administration of enoxaparin).
- Short-term prevention of VTE in Study 11356 (RECORD 3) (total knee replacement (TKR), 2-week administration of rivaroxaban and enoxaparin).

Rivaroxaban was administered once daily at an oral dose of 10 mg and compared with subcutaneously administered 40 mg enoxaparin once daily. The treatment duration in the RECORD 1 study was 35 ± 4 days for rivaroxaban and 36 ± 4 days for enoxaparin. The treatment duration in the RECORD 3 study was 12 ± 2 days for rivaroxaban and 13 ± 2 days for enoxaparin. Safety follow-up duration was 30 ± 5 days in both studies. The first dose of rivaroxaban was to be administered 6 to 8 h post-operatively, whereas the first dose of enoxaparin was to be administered pre-operatively. Day 1 was defined as the day of surgery. In RECORD 2 study, rivaroxaban was administered as 10 mg tablets once daily (od) every 24 ± 2 h up to Day 35 ± 4 (the day prior to venography). All subjects in the rivaroxaban treatment group additionally received enoxaparin placebo sc injections once daily in the evening, starting on Day 0 (day before surgery) and ending on Day 12 ± 2 (last dose).

The enoxaparin regimens are approved in Europe and the product is judged to be a relevant comparator.

Objectives
The primary objectives of the phase III trials were:

RECORD 1: To assess the efficacy and safety of rivaroxaban (BAY 59-7939) 10 mg once daily dosing compared with once daily subcutaneously administered enoxaparin 40 mg in extended prevention of VTE in men and women aged 18 years or above undergoing elective THR.

RECORD 2: Comparison of the efficacy and safety of VTE prophylaxis with rivaroxaban 10 mg once daily administered for 5 weeks to enoxaparin 40 mg once daily administered for 10-14 days followed by placebo up to Day 35 in men and women aged 18 years or above undergoing elective THR. The efficacy and safety parameters of primary interest were centrally adjudicated by Adjudication Committees.

RECORD 3: Assessment of the efficacy and safety of rivaroxaban (BAY 59-7939) 10 mg once daily dosing for the prevention of venous thromboembolic events (VTE) in male and female

subjects aged 18 years or above undergoing elective TKR.

Outcomes/endpoints
The efficacy and safety endpoints of the phase III studies were as follows:

RECORD 1:
The primary efficacy endpoint was a composite endpoint of:
- Any deep vein thrombosis (proximal and/or distal),
- Non-fatal pulmonary embolism,
- Death from all causes,

The analysis of the primary efficacy endpoint was solely based on the assessments made by the Venography and VTE Adjudication Committees.

The main safety endpoint was the incidence of treatment-emergent major bleeding observed not later than 2 days after last intake of study drug. Major bleeding observed after this period was considered separately.

RECORD 2:
The primary efficacy endpoint was defined as a composite endpoint of any DVT (proximal and/or distal) and non-fatal PE and death from all causes. The analysis of the primary efficacy endpoint (and all secondary efficacy endpoints related to VTE) was based solely on the assessments made by the Independent Central Adjudication Committee (ICAC) and VTE Adjudication Committees (AC/VTE).

The main safety endpoint was the incidence of treatment-emergent major bleeding observed not later than 2 days after last intake of study drug. Major bleeding observed after this period was to be considered separately. The analysis of the main safety endpoint was based solely on the assessment and classification made by the Bleeding Event Committee. Adverse events that started > 2 days after the last intake of study drug were not considered to be "treatment-emergent".

RECORD 3:
The primary efficacy endpoint was a composite endpoint of:

- Any DVT (proximal and/or distal),
- Non-fatal pulmonary embolism and,
- Death from all causes.

The analysis of the primary efficacy endpoint (and all secondary efficacy endpoints related to VTE) was based solely on the assessments made by the Independent Central Adjudication Committee (ICAC) and VTE Adjudication Committees (AC/VTE). The major secondary efficacy endpoint was the incidence of the composite endpoint comprising proximal DVT, non-fatal PE, and VTE-related death (i.e. "major VTE").

The main safety endpoint was the incidence of treatment-emergent major bleeding observed no later than 2 days after the last intake of study drug. Major bleeding observed after this period was assessed separately. The analysis of the primary safety endpoint was based solely on the assessment and classification made by the Bleeding Event Committee. Adverse events that started > 2 days after the last intake of study drug were not considered to be "treatment-emergent".

The definition of the primary endpoint is in agreement with the CHMP scientific advice received. Furthermore, a composite endpoint consistent with the CHMP guidance documents is included as the main secondary endpoint and all phase III trails followed recommendations given in the European guideline applicable at the time of product development ("Points to consider on clinical investigation of medicinal products for prophylaxis of intra- and post-operative venous thromboembolic risk"), now replaced by CPMP/EWP/707/98 ("Guideline on clinical investigations of medicinal products for prophylaxis of high intra- and post-operative venous thromboembolic risk").

For the pre-specified pooled analysis of the three pivotal studies the following composite endpoints were used additionally:

- Total VTE (Composite endpoint I), as defined for the individual studies.
- Major VTE (Composite endpoint III), as defined for the individual studies.
- Symptomatic VTE as defined for the individual studies.
- Symptomatic VTE or death, the composite of symptomatic DVT (proximal and distal), PE and death (from any cause).

In summary the over-all design of the pivotal studies is believed to be acceptable and similar to the pivotal studies on which the approval of other prophylactic agents within this area have been based

Sample size
In summary a population of more than 9500 subjects was enrolled in phase III studies, which investigated rivaroxaban 10 mg od in comparison to enoxaparin 40 mg od.

RECORD 1:
A total of 4541 subjects were randomized at 218 centres. 4433 subjects were treated with study medication (safety population); of these, 3153 were valid for the modified intent-to-treat (MITT) analysis, 3029 were valid for the per-protocol (PP) analysis.

RECORD 2:
A total of 2509 subjects were randomized at 123 centres. 2457 subjects were treated with study drug (safety population); of these, 1733 were valid for the modified intent to treat (MITT) analysis, 1615 were valid for the PP analysis.

RECORD 3:
A total of 2531 subjects were randomized at 147 centres. 2459 subjects were treated with study drug (safety population); of these, 1702 were valid for the MITT analysis, 1631 were valid for the PP analysis.

Randomisation
All subjects meeting the inclusion and none of the exclusion criteria were eligible for randomization. For randomization, an interactive voice response system (IVRS) was used. The randomization was done stratified by centre using permuted blocks: the centre-balancing list used internally by the IVRS provider to determine the randomized treatment assignment (stratified by centre) and the list of random numbers used for packaging and labelling of the medication.

Blinding (masking)
All studies had a double-blind, double-dummy design. The packaging and dosage were performed to ensure that the treatments between the different groups appeared identical. Subjects, investigators, and sponsor/contract research personnel remained blinded as to which study drug was administered. The Steering Committee, the Independent Central Adjudication Committee**,** the VTE Adjudication Committee, the Cardiovascular Event Adjudication Committee, and the Bleeding Event Adjudication Committee performed their assessments in a blinded manner. The DSMB reviewed unblinded data.

Statistical methods
All variables were analyzed descriptively with appropriate statistical methods: categorical variables by frequency tables and continuous variables by sample statistics (i.e. mean standard deviation, minimum, median, quartiles, and maximum). If not mentioned otherwise, all statistical tests were performed 2-sided with a type I error rate of α=5%.

In the studies in hip surgery, study RECORD 1 and RECORD 3, efficacy was assessed in two steps. First, a non-inferiority test was performed based on the PP population. If non-inferiority was shown, a superiority test was to be performed subsequently based on the modified ITT (MITT) population. In study RECORD 2, the primary efficacy analysis was performed in subjects valid for MITT analysis testing for superiority. The PP analysis was performed as a supportive analysis.

Pooled analyses were pre-specified for symptomatic events during treatment until day 12 ± 2 in subjects valid for safety. This time point was chosen because it represents the treatment duration shared by the active treatment schedules of all 3 studies. Also, symptomatic events can be assessed continuously throughout the study in contrast to the endpoints “total VTE” and “major VTE”, which include asymptomatic components which were documented by venography at the end of the treatment phase. For the assessment of efficacy in subpopulations, the endpoints “total VTE” and “major VTE” were evaluated in pooled MITT analyses. All pooled efficacy analyses used exact study-stratified methods for the odds-ratio as a measure of treatment effect.

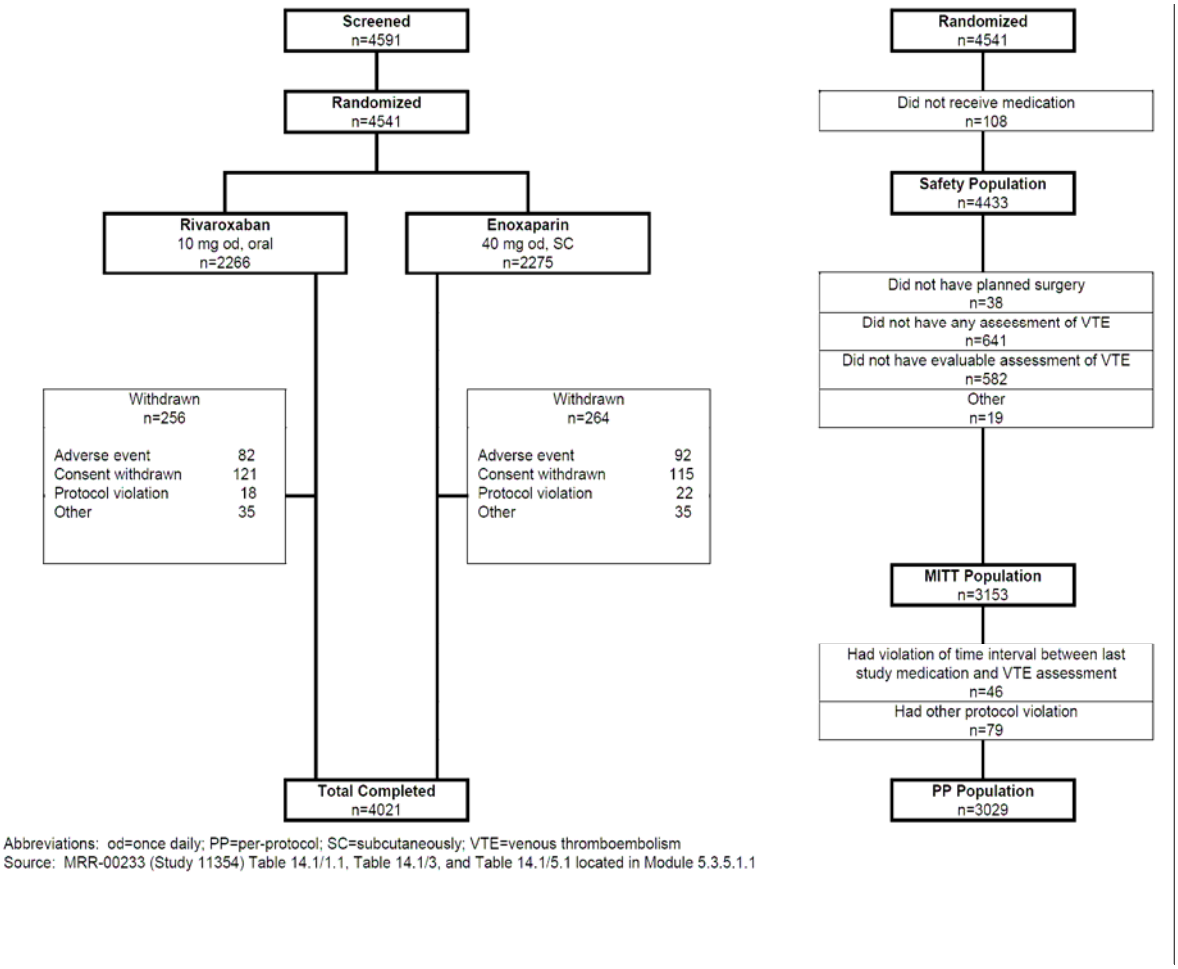
Demographic variables and baseline characteristics were summarized by treatment group for all 3 analysis populations. Medical history findings and adverse events were coded by MedDRA codes and medications by ATC codes. Treatment group comparability was checked for each of the three analysis populations. This comparison was done with respect to age, height, weight, and body mass index univariately by 2-way analyses of variance. Categorical variables like gender and race were analyzed by a Cochran-Mantel-Haenszel test adjusted for geographic region.

No interim analysis had been planned. However, there was an ongoing safety and efficacy monitoring by the DSMB who decided to review unblinded data. In case of an unacceptable efficacy and/or safety profile seen in any of the two treatment arms, the DSMB could have recommended to the Steering Committee the prematurely stop of the trial.

RESULTS

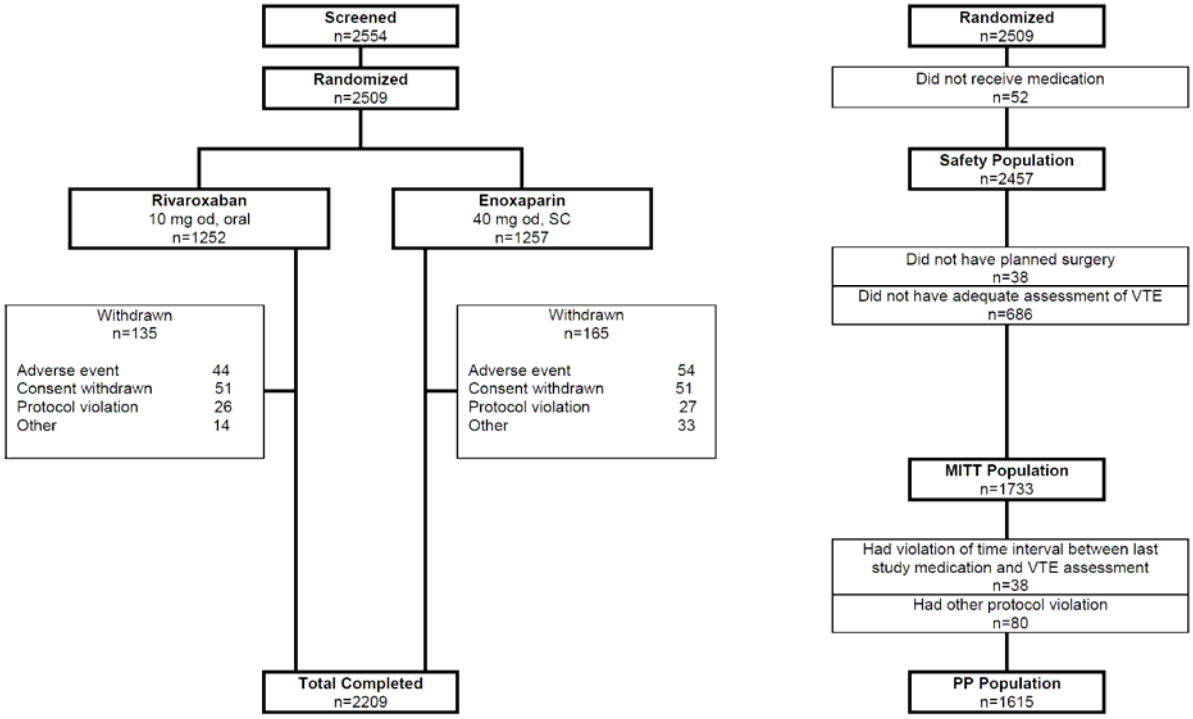
Participant flow

Study RECORD 1



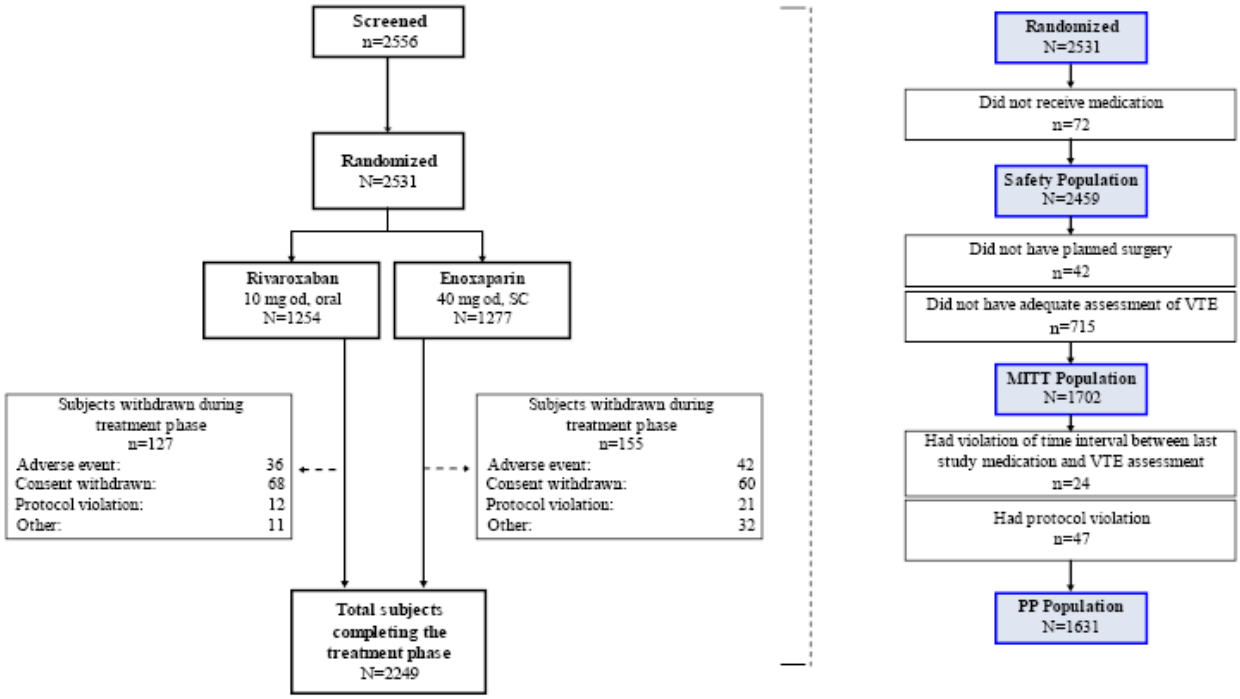
Abbreviations: od=once daily; PP=per-protocol; SC=subcutaneously; VTE=venous thromboembolism
Source: MRR-00233 (Study 11354) Table 14.1/1.1, Table 14.1/3, and Table 14.1/5.1 located in Module 5.3.5.1.1

Study RECORD 2



Abbreviations: MITT = modified intent-to-treat; od=once daily; PP=per-protocol; SC=subcutaneously; VTE=venous thromboembolism
Source: Table 14.1/1.1, Table 14.1/3, and Table 14.1/5.1

Study RECORD 3



Recruitment
Pivotal studies were conducted in Europe, Australia, USA, Canada, Asia, Latin and South America.
RECORD 1: 07 Feb 2006 – 13 Mar 2007 (218 sites)
RECORD 2: 19 Feb 2006 – 26 Jun 2007 (123 sites)
RECORD 3: 21 Feb 2006 – 18 Jan 2007 (147 sites)
Recruitment consistency across all regions was confirmed.

Conduct of the study
The original protocol for RECORD 1was amended 4 times, three amendments included only minor or editorial changes. Amendment 1 was a major amendment applicable to all participating countries and introduced a few major changes: adjudication by the AC/VTE refers to all symptomatic DVTs during treatment and follow-up, modification of the term "significant liver disease" in the list of exclusion criteria, elaboration on stopping rules related to liver function, addition of "net clinical benefit" assessed by the composite endpoint comprising major VTE and treatment-emergent major bleeding as a secondary efficacy endpoint, addition of "incidence of surgical site bleedings associated with ≥2 g/dL fall in haemoglobin or leading to infusion of ≥2 units of whole blood or packed cells" as a safety variable, introduction of univariate comparison by 2-way analysis of variance to check treatment group comparability, introduction of the "modified ITT" population for efficacy analysis according to ICH-E9 Guideline, amendments to the primary efficacy analysis, which was to be performed in the PP population instead of the ITT population. The modified ITT analysis was specified as the next step in a hierarchical analysis plan. The PP population was the primary population for non-inferiority test and the modified ITT population was the primary population for the superiority test. New assumptions were made for the non-inferiority testing, e.g. it was to be performed in the PP population primarily.

The original protocol of study RECORD 2 was amended once. Amendment 1 was major, applicable to all participating countries. In addition to some minor editorial or administrative changes, the amendment introduced a few major changes including the change of visit timing from Day 7 ± 2 to Day 6 ± 2, inclusion of clinical chemistry sample at Day 6 and liver enzyme monitoring and stopping rules.

Apart from the amendment, an additional change related to the data analysis was implemented: Although the protocol-specified time period to perform venography was 31 to 39 days following surgery (Day 36 ± 4), this time window was widened to 29 to 41 (Day 36 ± 6) days at the Blind Review Meeting to allow for a greater number of venographies to be included in the analysis. In addition, this time window was also widened to 29 to 41 (Day 36 ± 6) for symptomatic VTE/death.

The original protocol for the RECORD 3 study was amended four times; three amendments included only minor or editorial changes. Amendment 1 was a major amendment applicable to all participating countries and was performed before inclusion of the first patient. Amongst the major changes were: change in blood sampling from Day 7 ± 2 to Day 6 ± 2, adjustment of liver enzyme monitoring and study drug discontinuation rules related to liver function test abnormality, addition of the incidence of surgical site bleeding associated with ≥2 g/dL fall in haemoglobin or leading to infusion of ≥2 units of whole blood or packed cells as an additional safety variable, modification of the term "significant liver disease", addition of retention samples to be taken (HIV-, hepatitis A, B, and C-serology) for those subjects who had provided additional consent, for missing or venographies that were not performed or evaluable, measures were added to collect the reason for why the test was not done or not evaluable, clarification in the statistical analysis plan concerning study objective for US submission, removal of the enoxaparin 30 mg bid dose option (change implemented prior to enrolment of first subject).

Overall, the protocol amendments seem to have been appropriately performed and are judged not to affect the integrity of the studies.

Baseline data
The treatment groups in studies RECORD 1, 2 and 3 were fairly well balanced and the study populations are judged to be reasonably representative for a target population undergoing elective surgery. Approximately 60 % of the patients in the hip study and 65 % in the knee study had the surgery performed under regional anaesthesia. Considering that rivaroxaban is given orally, it is of

interest to note that the differences between the treatment groups with regard to the primary endpoint seen in patients undergoing surgery under general anaesthesia were consistent with the overall results.

The demographic data were provided for each subgroup in the relevant treatment arm with respect to gender, race, age, weight and BMI. The study populations are reasonably representative of the European target population. The proportion of females was 55.5% in RECORD 1, 54% in RECORD 2 and 68% in RECORD 3 study. The mean age was 63, 61.5 and 67.6 years with approximately 13, 13.2 and 21% being >75 years of age, in the RECORD 1, RECORD 2 and RECORD 3 trial, respectively. These data do not suggest relevant baseline differences indicated by the homogeneity testing in PP, MITT and safety population analysis.

Numbers analysed

The number of patients per treatment arm was adequately reported for each pivotal study including the information on patients who discontinued the treatment and did not complete the protocol.

Efficacy data were obtained from 3029 (PP analysis) of the 4541 randomized subjects in the RECORD 1 study. For the MITT analysis 3153 subjects were valid.

In the RECORD 2 study, the primary efficacy endpoint was obtained from the MITT population which comprised 1733 subjects of the 2509 randomized subjects. 1615 patients were valid for the PP analysis.

Efficacy data were obtained from 1631 (PP analysis) of the 2531 randomized subjects in the RECORD 3 study. For the MITT analyses 1702 subjects were included.

The numbers of withdrawals as well as the reasons for withdrawal were balanced between the treatment groups with the exception of an apparent imbalance in the number of evaluable venograms between the treatment groups in RECORD 1 and RECORD 3. Approximately 89% and 88% of the randomised patients completed treatment in the hip and knee study, respectively, which appears to be in line with what could be expected in well performed studies. The observed rate of invalid venograms ranged between 26.9% (RECORD 1) and 28.2% (RECORD 3) of the randomised patients. The number of patients who did not have any VTE assessment (no venogram performed) does not seem to be significantly high.

Outcomes and estimation

The extended and short-term prevention regimens tested in trials RECORD 1 and RECORD 3 reflect current practice as recommended by treatment guidelines. These guidelines recommend thromboprophylaxis of at least 10 days for subjects undergoing THR or TKR and extended prophylaxis for up to 35 days after surgery in subjects undergoing THR. RECORD 2 study compared extended prevention with rivaroxaban *vs* short-term prevention with enoxaparin. Different durations of thromboprophylaxis for the comparator in studies RECORD 1 and RECORD 2 reflect different standards of care in different countries and regions related to the use of low molecular weight heparins.

The results for the primary efficacy endpoint and its components are given in the following tabular overviews for the MITT and PP population.

Pair-wise comparisons for the primary efficacy endpoint

	Incidence		Mantel-Haenszel-weighted difference to enoxaparin		*P* value [b] H_0: difference = 0%
	Point estimate	95% CI[a]	Point estimate	95% CI[a]	
RECORD 1 Hip surgery					
PP population					
Primary efficacy endpoint					
Rivaroxaban 10 mg od	0.9%	[0.5%, 1.4%]	-2.53%	[-3.55%, -1.51%]	<0.001
Enoxaparin 40 mg od	3.4%	[2.5%, 4.4%]			
MITT population					
Primary efficacy endpoint					
Rivaroxaban 10 mg od	1.1%	[0.7%, 1.8%]	-2.62%	[-3.69%, -1.54%]	<0.001
Enoxaparin 40 mg od	3.7%	[2.8%, 4.8%]			
RECORD 3 Knee surgery					
PP population					
Primary efficacy endpoint					
Rivaroxaban 10 mg od	9.3%	[7.4%, 11.6%]	-8.70%	[-11.97%, -5.44%]	<0.001
Enoxaparin 40 mg od	18.1%	[15.6%, 20.9%]			
MITT population					
Primary efficacy endpoint					
Rivaroxaban 10 mg od	9.6%	[7.7%, 11.8%]	-9.15%	[-12.40%, -5.89%]	<0.001
Enoxaparin 40 mg od	18.9%	[16.4%, 21.7%]			

a Confidence intervals for proportions were calculated using exact methods. Confidence intervals for weighted differences were calculated using asymptotic methods, with weights based upon sample sizes per strata (geographic region).
b *P* values (2-sided) were calculated based on the Mantel-Haenszel weighted estimator and its variance estimate.
Abbreviations: CI=confidence interval; MITT=modified intent to treat; PP=per protocol

On the background of MITT incidence rates of 3.7% and 18.9% in the comparator groups in the RECORD 1 and RECORD 3 trials, respectively, absolute reductions of 2.6 and 9.2%, respectively, appear statistically significant and therapeutically impressive. The higher incidence in the knee replacement study (especially for distal thrombi) is in line with the earlier experience.

Incidence of the primary efficacy endpoint and its individual components (MITT population)

	RECORD 1		RECORD 3	
Endpoint/component	**Rivaroxaban 10 mg od (N=1595) n (%)**	**Enoxaparin 40 mg od (N=1558) n (%)**	**Rivaroxaban 10 mg od (N=824) n (%)**	**Enoxaparin 40 mg od (N=878) n (%)**
Primary efficacy endpoint				
Any event	18 (1.1)	58 (3.7)	79 (9.6)	166 (18.9)
Death (any cause)	4 (0.3)	4 (0.3)	0 (0.0)	2 (0.2)
Nonfatal PE	4 (0.3)	1 (<0.1)	0 (0.0)	4 (0.5)
Proximal and/or distal DVT	12 (0.8)	53 (3.4)	79 (9.6)	160 (18.2)
Components				
Death (VTE related)	0 (0.0)	1 (<0.1)	0 (0.0)	0 (0.0)
Death (not VTE related)	2 (0.1)	3 (0.2)	0 (0.0)	0 (0.0)
Death (unexplained)	2 (0.1)	0 (0.0)	0 (0.0)	2 (0.2)
DVT, proximal	1 (<0.1)	31 (2.0)	9 (1.1)	20 (2.3)
DVT, distal	12 (0.8)	27 (1.7)	74 (9.0)	156 (17.8)

Abbreviations: MITT=modified intent-to-treat; od=once daily; PP=per protocol; PE=pulmonary embolism; DVT=deep vein thrombosis; VTE=venous thromboembolism

Main secondary endpoint: Pair-wise comparisons for Major VTE

	Incidence		Mantel-Haenszel-weighted difference to enoxaparin		*P* value [b] H_0: difference = 0%
	Point estimate	95% CI [a]	Point estimate	95% CI [a]	
RECORD 1 Hip surgery					
MITT population					
Primary efficacy endpoint					
Rivaroxaban 10 mg od	0.2%	[0.1%, 0.6%]	-1.74%	[-2.45%, -1.03%]	<0.001
Enoxaparin 40 mg od	2.0%	[1.4%, 2.8%]			
RECORD 3 Knee surgery					
MITT population					
Primary efficacy endpoint					
Rivaroxaban 10 mg od	1.09%	[0.5%, 1.9%]	-1.59%	[-2.80%, -0.38%]	0.010
Enoxaparin 40 mg od	2.6%	[1.7%, 3.8%]			

In the RECORD 1 study, in 3153 subjects valid for MITT analysis, the composite primary efficacy endpoint "total VTE" (composite endpoint I) outcome occurred in 18 (1.1%) and 58 (3.7%) of subjects randomized to rivaroxaban or enoxaparin, respectively with a statistically significant difference (P<0.001). This finding clearly demonstrated the superiority of rivaroxaban over enoxaparin in preventing VTE. The relative risk reduction (unweighted relative risks) was 69.7% for the primary efficacy endpoint for the MITT population. Most components of the primary composite efficacy endpoint were numerically reduced in the presence of rivaroxaban compared with enoxaparin, including proximal DVT, distal DVT, VTE-related death and non-VTE-related death in the MITT population. Only numerical differences were observed for death of any cause between the 2 treatments (rivaroxaban 4 (0.3%) subjects, enoxaparin 4 (0.3%) subjects) and nonfatal PEs, which were observed in 4 (0.3%) subjects receiving rivaroxaban compared to 1 (<0.1%) subject in the enoxaparin group. Furthermore unexplained death occurred in 2 (0.1%) and 0 (0%) subjects in the rivaroxaban and enoxaparin groups, respectively.

Major VTE, the main secondary efficacy endpoint, occurred in 4 (0.2%) subjects receiving rivaroxaban 10 mg od compared to 33 (2.0%) subjects receiving enoxaparin 40 mg od thus demonstrating superiority over enoxaparin (P<0.001; MITT analysis of major VTE).

Rivaroxaban was statistically superior to enoxaparin in reducing the incidence of composite primary endpoint (VTE-related death, nonfatal PE, and DVT) and composite main secondary endpoint (proximal DVT, nonfatal PE, and all-cause death). According the analysis of net clinical benefit which was the composite of major VTE and treatment-emergent major bleeding the rivaroxaban regimen was statistically superior to the enoxaparin regimen.

The CHMP raised a concern with respect to the invalidity rates in all pivotal trials resulting from missing/unevaluable venograms in the study A description of the reasons for not performing the scheduled venographies was provided in the respective study reports. Of the subjects invalidated because of inadequate assessment of thromboembolism, between 45.0% and 52.4% did not have any venography. Main reason was a premature termination of participation in the trial (between 17.6% and 26.0% of all subjects with inadequate assessment if thromboembolism), followed by failed venipuncture (between 9.4% and 11.3%) and subject's refusal of venography (between 3.0% and 11.2%). Further re-examination of these cases revealed that the reasons for the venograms not being performed or being assessed as non-evaluable are as expected for this type of trial. There is no apparent imbalance between the treatment arms with regard to those reasons. The rather high level of discordance between the central adjudication, using strict criteria, and the local investigators interpretation is in line with what has been observed in other similar studies and supports the strategy to use the blinded central adjudication for the primary efficacy evaluation.

In the RECORD 2 study, the composite primary efficacy endpoint occurred in 17 (2.0%) and 81 (9.3%) of subjects randomized to rivaroxaban or enoxaparin, respectively. Thus the rivaroxaban regimen was found superior to the enoxaparin regimen.

All components of the primary composite efficacy endpoint were reduced in the rivaroxaban regimen compared with the enoxaparin regimen, including proximal DVT (5 (0.6%) subjects *vs* 44 (5.1%) subjects), distal DVT (11 (1.3%) *vs* 49 (5.6%) subjects), nonfatal PE (1 (0.1%) *vs* 4 (0.5%) subjects), and death (2 (0.2%) *vs* (60.7%) subjects). For the main secondary efficacy endpoint, major VTE, the rivaroxaban regimen (6 subjects (0.6%)) was statistically superior to the enoxaparin regimen (49 subjects (5.1%)); (P<0.001; MITT analysis of major VTE). For symptomatic VTE, the rivaroxaban regimen (3 subjects (0.4%)) was statistically superior to the enoxaparin regimen (15 subjects (1.7%)).

Thus, in RECORD 2 a superior efficacy of a five week regimen with rivaroxan as compared to a two week regimen with enoxaparin is demonstrated.

In the RECORD 3 study, the efficacy data were obtained from 1631 (PP) of the 2531 randomized subjects. Based on the non-inferiority margin of 4%, results for the composite primary efficacy endpoint demonstrated that the objective of non-inferiority against enoxaparin was met and that rivaroxaban was at least as effective as enoxaparin in preventing VTE. In 1702 MITT subjects, the composite primary efficacy endpoint outcome occurred in 79 (9.6%) and 166 (18.9%) of subjects randomized to rivaroxaban or enoxaparin, respectively; a statistically significant difference (P<0.001) was observed. This finding demonstrated the superiority of rivaroxaban over enoxaparin in preventing VTE. The relative risk reduction (unweighted relative risks) was 49.3% for the primary efficacy endpoint in the MITT population. All components of the primary composite efficacy endpoint were reduced in the presence of rivaroxaban compared with enoxaparin, including proximal DVT, distal DVT, nonfatal PE and death (MITT population).

For symptomatic VTE, rivaroxaban demonstrated superior efficacy with a lower incidence rate when compared with enoxaparin. In the PP and MITT analyses, rivaroxaban was statistically superior to enoxaparin in the incidences of composite endpoint (DVT, nonfatal PE, and VTE-related death), as for the composite endpoint (proximal DVT, nonfatal PE, and all-cause death). For the primary efficacy endpoint, superiority of rivaroxaban *vs* enoxaparin was demonstrated by a consistently lower incidence of DVT, both for proximal and distal DVT. In addition, incidence rates for the components death and nonfatal PE were also lower in subjects receiving rivaroxaban compared to those receiving enoxaparin. For the main secondary efficacy endpoint "major VTE", superiority of rivaroxaban *vs* enoxaparin was mainly driven by a lower incidence of proximal DVT. The overall results are consistent for the primary efficacy endpoint "total VTE" and the main secondary efficacy endpoint "major VTE". This study seems to have demonstrated superiority of rivaroxaban to enoxaparin concerning efficacy in patients undergoing knee surgery as an example for major orthopedic surgery of the lower limb.

The results of other secondary end-points were also in line with the primary efficacy results.

Furthermore during heterogeneity testing a statistically significant difference female gender was apparent and the meaning of this finding in the context of the study results is unclear. To further explore the effect of gender on the primary efficacy endpoint, a logistic regression model was employed including the interaction of treatment with gender. The test for interaction of treatment with gender was not statistically significant in either the PP or MITT populations.

The clinical phase III program demonstrated the superiority of rivaroxaban *vs* enoxaparin concerning efficacy in the direct short term treatment comparison, the direct extended treatment comparison as well as the comparison of extended treatment with rivaroxaban *vs* short-term treatment with enoxaparin. There is a clear superiority of rivaroxaban 10mg od to standard comparator enoxaparin 40mg od in the prevention of venous thromboembolism in patients undergoing major orthopaedic surgery of the lower limb.

- Analysis performed across trials (pooled analyses)

The main purpose of the meta-analyses is the investigation of the treatment effect in the different subpopulations of clinical relevance. The pooled efficacy data for the three RECORD studies

provided, including RECORD 2 which is regarded as a supportive study. Since the two treatment arms in RECORD 2 differ both with regard to treatment time and prophylactic agent used these pooled efficacy analyses are believed to be of less interest. The p-value for heterogeneity indicates substantial differences between the estimated treatment effects in the three studies, which is not implausible given the differences in indication and design.

In the overall population of the 3 pivotal studies, rivaroxaban was generally more effective than enoxaparin in preventing total VTE (MITT analysis) in nearly all subpopulations. These subpopulations with an observed odds ration less than the upper 95% CI limit of the overall population estimate (0.44) were: both genders, white and Asian race, all age groups, bodyweight >50 to 110 kg, BMI groups between 18.5 kg/m2 to <40 kg/m2, general anesthesia and regional anesthesia, duration of surgery, absence and presence of risk factors for VTE, absence and presence of a history of VTE, creatinine clearance between 30 to <50 mL/min and >80 mL/min, fragile subjects, and a limited number of subjects taking CYP3A4 or P-gp inducers.

- Clinical studies in special populations

No clinical studies were performed in children; rivaroxaban was only studied in patients older than 18 years. Rivaroxaban is not recommended for use in patients below 18 years of age. There is no clinically relevant difference in rivaroxaban pharmacokinetics between men and women.

As stated above under clinical pharmacokinetics, rivaroxaban exposure increases with increased age, reduced renal function and reduced hepatic function.

Based on the data observed in the renal impairment PK study and in the phase III trials, the use of rivaroxaban is not recommended in patients with creatinine clearance <15 ml/min and the product is only be used with caution in patients with severe renal impairment or patients with moderate renal impairment concomitantly receiving other medication increasing rivaroxaban plasma concentrations. This is reflected in the SPC.

The AUC of rivaroxaban was increased by 127% in moderate hepatic impairment (cirrhotic subjects classified as Child Pugh B). A significantly altered sensitivity in anti-coagulant activity towards rivaroxaban plasma exposure (increase in slope for PT/rivaroxaban plasma concentration relationship by more than 2 fold) was observed . A considerably larger increase in exposure could be expected in patients with severe hepatic impairment. As stated in the SPC, rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and a clinically relevant bleeding risk. In addition, caution is advised in the treatment of patients with other hepatic disease of moderate grade.

- Supportive studies

No supportive studies were provided, although the RECORD 2 study might be considered as supportive given the differences in the use of the prophylactic agents and the treatment duration. For the purpose of the overall efficacy and safety overview of the product, the study is described along with the main RECORD 1 and RECORD 3 studies.

Clinical safety

Introduction

The main safety endpoint during phase II and III studies was the incidence of treatment emergent major bleeding observed not later than 2 days after last intake of study drug. Major bleeding observed after this period was considered separately. Bleeding events were analysed and assessed by an independent Adjudication Committee/Bleeding Events (AC/BE). The same AC/BE assessed all of the three studies of phase III with the same members and the same consistent method. The analysis of the primary safety endpoint was solely based on the classification made by the Committee. Adverse events that started more than 2 days after the last intake of study drug were not considered to be "treatment-emergent".

Other safety variables included:

- Major bleeding observed after this period was considered separately.
- Incidence of any treatment-emergent bleeding observed not later than 2 days after last intake of study drug.
- Incidence of non-major treatment-emergent bleeding including non-major clinically significant bleeding observed not later than 2 days after last intake of study drug.
- Incidence of (any, non-major, major) post-operative bleeding (the post-operative period started 6 h after end of surgery or with the first post-operative intake of study medication, whatever came first and ended 2 days after last intake of study medication).
- Incidence of surgical site bleedings associated with ≥2 g/dL fall in haemoglobin or leading to transfusion of ≥2 units of whole blood or packed red blood cells.
- Treatment-emergent adverse events.
- Treatment-emergent serious adverse events.
- Deaths.
- Adverse events starting more than 2 days after stop of treatment.
- Adjudicated cardiovascular events (on treatment/off treatment).
- Incidence of (prolonged) hospitalization.
- Transfusion requirements.
- Discontinuations due to adverse events.
- Amount of intra-operative blood loss.
- Post-operative drainage volume.
- Laboratory parameters.

An additional evaluation of bleeding events was conducted in accordance with the Scientific Advise given by the CHMP. In addition to the specified bleeding categories in phase III studies, the extended category of major bleeding events removing the restriction to the extra-surgical site for a fall in haemoglobin of > 2g/dL or for bleeding leading to infusion of ≥2 units of whole blood or packed cells was applied.

The safety of rivaroxaban in these studies was evaluated by documentation of adverse events coded according to Medical Dictionary for Regulatory Activities (MedDRA) conventions and laboratory testing. ECG monitoring was performed and analysed for phase I and for the phase II studies in the indication VTE prevention. Additionally, assessment of cardiovascular events was provided by the Adjudication Committee/cardiovascular event for all studies.

- Patient exposure

Safety data for rivaroxaban have been derived from studies completed and reported with a cut-off date of 31 August 2007.

No safety signals were identified from data analysis of phase I studies.

The phase II study programme included different doses up to 60 mg tdd and was the basis of the decision for further use of rivaroxaban 10 mg od in the phase III VTE prevention studies. Four VTE prevention studies and two VTE treatment studies were evaluated for the pooled safety analysis of phase II studies. This comprised data from 2787 subjects enrolled in VTE prevention studies, out of which 2232 subjects received rivaroxaban and 555 subjects received enoxaparin. A total of 1146 subjects valid for safety were enrolled in VTE treatment studies; 883 subjects received rivaroxaban and 263 comparator treatment. The number of subjects in phase II with the target dose of 10 mg rivaroxaban od was low, treatment durations were different and the safety profile in phase II was comparable to phase III. Bleeding rates observed with different rivaroxaban doses in the dose-finding studies are discussed in the section Dose-response studies.

In the three phase III trials, a total of 1220 subjects were treated with rivaroxaban 10 mg od for a period of approximately 2 weeks, and 3437 subjects for a period of approximately 5 weeks. Safety data from phase III were derived from three pivotal studies (RECORD1, RECORD 2 and RECORD3), all of which were designed for patients receiving rivaroxaban 10 mg od. Thus, it is suitable to pool the

results from these methodologically consistent studies to conduct a safety analysis. All three phase III studies were assessed consistently. Bleeding events were analysed and evaluated by an independent Adjudication Committee. The total exposure to prophylactic treatment with rivaroxaban 10 mg appears to be sufficient in order to reasonably characterise the safety profile of the proposed dosing regimen.

Overview of completed clinical studies of phase II and phase III

Study details Phase / Study Number	Comparator	Subjects randomized (N)	Safety population (N)	Subjects on rivaroxaban 10 mg od (N)	Scheduled duration of treatment[c]
VTE prevention					
Phase II					
10942	Enox 40	641	625	80[a]	8±2 days
10944	Enox 40	722	704	136[a]	9±2 days
10945	Enox 30	621	613	102[a]	8±2 days
11527	Enox 40	873	845	142	9±2 days
Phase III					
11354	Enox 40	4541	4433	2209	35±4 days
11356	Enox 40	2531	2459	1220	12±2 days
11357	Enox 40	2509	2457	1228	35±4 days[b]
VTE treatment					
Phase II					
11223	Enox/VKA	613	604	na	12 weeks
11528	Heparin/VKA	543	542	na	12 weeks

a Listed in this category although actually the dose was rivaroxaban 5 mg bid
b The treatment duration of 35±4 days applied for rivaroxaban treatment, whereas the treatment duration for enoxaparin treated subjects was 13±2 days
c Scheduled treatment refers to treatment with rivaroxaban
Abbreviations: bid = twice a day; Enox 30 = Enoxaparin 30 mg bid; Enox 40 = Enoxaparin 40 mg od ; Enox/VKA = Enoxaparin followed by vitamin K antagonist; Heparin/VKA = heparin treatment followed by vitamin K antagonist; N/A = not applicable; VTE = venous thromboembolism

Based on the demographic data analysis, no differences between the treatment groups within two indications during investigation in phase II were obvious. The gender distribution was 60% women *vs* 40% men for the rivaroxaban treated subjects in VTE prevention studies and 44% women *vs* 56% men for the rivaroxaban treated subjects in VTE treatment studies. The race distribution is typical for a European population with more than 90% of white race in studies for both indications. About one third of the patients had a body mass index (BMI) of 30 kg/m2 or higher in the VTE prevention studies and the respective number in the VTE treatment studies was 26% for the rivaroxaban treated subjects. Mean age of the subjects was approximately 64 years with nearly half of the subjects younger than 65 years but only about 3 % of the subjects aged 40 years and younger. Although the mean body mass index of approximately 28 kg/m2 was within the normal range, about one third of the subjects had a BMI > 30 kg/m2.

Risk factors for thromboembolism were evenly distributed between treatment groups. In general, the profile of medical history findings appropriate to the population studied in relation to their age profile. When comparing the medicinal history of population with THR and with TKR, differences between both groups can be explained by the higher age of the subjects who had undergone TKR. The most noticeable difference between the hip replacement population and in the TKR population was observed in the surgical and medical procedures (51% *vs* 61%), metabolism and nutrition disorders (23% *vs* 34%) and vascular disorders (48% *vs* 62%). These differences are explained by the demographic variables, such as age, gender and BMI, which were different between the populations.

Thromboembolism Risk Factors of Subjects in Rivaroxaban phase III Studies

	Rivaroxaban 10 mg od (N = 4657)	Enoxaparin/ Placebo (N = 4692)	Total (N = 9349)
Any risk factor related to medical history, n (%)			
Yes	362 (8%)	378 (8%)	740 (8%)
Active malignancy, n (%)			
Yes	34 (1%)	29 (1%)	63 (1%)
Heart failure, n (%)			
NYHA I	24 (1%)	14 (<1 %)	38 (<1 %)
NYHA II	30 (1%)	47 (1%)	77 (1%)
NYHA III	7 (<1 %)	10 (<1 %)	17 (<1 %)
NYHA IV	0 (0%)	1 (<1 %)	1 (<1 %)
NYHA unknown	18 (<1 %)	11 (<1 %)	29 (<1 %)
History of deep venous thrombosis, n (%)			
Yes	94 (2%)	104 (2%)	198 (2%)
History of pulmonary embolism, n (%)			
Yes	17 (<1 %)	25 (1%)	42 (<1 %)
Severe varicosis, n (%)			
Yes	173 (4%)	172 (4%)	345 (4%)
Thrombophilia (hereditary/acquired), n (%)			
Yes	6 (<1 %)	3 (<1 %)	9 (<1 %)

In summary, the adverse event safety assessment is based mainly on the safety population in phase III studies, which comprises of 4657 subjects randomised to rivaroxaban and 4692 subjects randomised to enoxaparin, since the number of subjects in phase II with the target dose of 10 mg rivaroxaban od was low and the treatment durations were different. In addition, there were no apparent differences concerning the type of adverse events between all phases of the clinical programme.

Safety data with regard to the long term administration are missing, but since rivaroxaban is currently indicated for short time use (<35 days), the safety evaluations are appropriate.

- Adverse events

In the phase I studies 36.1% of all subjects who received rivaroxaban in any study reported at least one treatment emergent adverse event, compared to 27.1% in the placebo group. The majority of adverse events (30.4%) observed following rivaroxaban administration were of mild intensity, 5.6% were of moderate, and <0.2% were of severe intensity. The most frequent adverse event observed in Phase I trials was headache, which is commonly observed in phase I trials regardless of the test drug. Overall, no specific safety signals could be identified from the data for adverse events in clinical pharmacology trials in phase I. However, as most of these comprised of single dose drug administration, this is an expected result.

The tendency to increased incidences of headache and gastrointestinal symptoms reported in the phase I studies was weaker in the phase II programme. No unexpected severe adverse events were recorded. Overall, the compiled safety data of adverse events from short term phase II VTE prevention studies and from phase II VTE treatment studies with a median treatment duration of 84 days presented similar safety profiles between the two indications and between rivaroxaban and the comparator. The respective incidence rates were not different between the treatment groups.

The most common treatment-emergent adverse event from pooled data of the three phase III studies were gastrointestinal disorders, followed by general disorders and administration site conditions and injury, poisoning, and procedural complications. Although the three phase III studies include different indications (THR *vs* TKR) and different treatment durations (2 week active treatment with rivaroxaban and enoxaparin in RECORD 3, 5 week active treatment with rivaroxaban and enoxaparin in RECORD 1 and 2 week active treatment with enoxaparin followed by placebo *vs* 5 week active treatment with rivaroxaban in RECORD 2) the adverse event rates are consistent across the three studies. Concomitant medications taken during the 2 week screening period prior to the surgery day were

evenly distributed between treatment groups in both populations. Approximately 9% of the patients were taking antithrombotic medication, such as aspirin, and 25% used anti-inflammatory drugs. Furthermore, around 28 % of patients were taking agents acting on the renin-angiotensin system, 15% of patients took beta-blockers, 15% of patients were treated with lipid-reducing agents and 12% with calcium channel blockers. The number of patients on concomitant medication is believed to be appropriate and supportive of the conclusion that the populations studied were representative of the target population with regard to comorbidity.

Generally, the incidence of adverse events was similar between the treatment groups. Differences between the treatment groups did not exceed 1%. No group differences were seen between the most frequently reported treatment-emergent adverse events in both treatment groups with regard to the observed gastrointestinal symptoms (nausea, vomiting, and constipation), general disorders (pyrexia), procedural complications (postoperative anaemia, procedural pain). Amongst the most frequently reported adverse events in the rivaroxaban patient group were oedema, muscle spasm, pain in extremities, skin blisters and pruritus. The treatment emergent adverse events and their frequencies are adequately reflected in the SPC.

Incidence of common (> 1%) treatment-emergent adverse events until day 12±2 (pooled data from phase III studies)

Primary System Organ Class Preferred Term	Rivaroxaban (N = 4657)	Enoxaparin/placebo (N = 4692)
Any system organ class		
Any event	2957 (63.5%)	3090 (65.9%)
Blood and lymphatic system disorders		
Any event	262 (5.6%)	264 (5.6%)
Anaemia	192 (4.1%)	196 (4.2%)
Cardiac disorders		
Any event	192 (4.1%)	195 (4.2%)
Tachycardia	53 (1.1%)	56 (1.2%)
Gastrointestinal disorders		
Any event	1197 (25.7%)	1250 (26.6%)
Abdominal pain upper	49 (1.1%)	38 (0.8%)
Constipation	318 (6.8%)	335 (7.1%)
Diarrhoea	105 (2.3%)	137 (2.9%)
Dyspepsia	37 (0.8%)	49 (1.0%)
Nausea	517 (11.1%)	519 (11.1%)
Vomiting	452 (9.7%)	482 (10.3%)
General disorders and administration site conditions		
Any event	720 (15.5%)	730 (15.6%)
Chest pain	34 (0.7%)	54 (1.2%)
Oedema peripheral	193 (4.1%)	162 (3.5%)
Pyrexia	400 (8.6%)	406 (8.7%)
Infections and infestations		
Any event	305 (6.6%)	312 (6.7%)
Urinary tract infection	82 (1.8%)	90 (1.9%)
Injury, poisoning, and procedural complications		
Any event	732 (15.7%)	699 (14.9%)
Anaemia postoperative	174 (3.7%)	167 (3.6%)
Procedural hypotension	47 (1.0%)	34 (0.7%)
Procedural pain	158 (3.4%)	159 (3.4%)
Wound secretion	129 (2.8%)	93 (2.0%)
Investigations		
Any event	562 (12.1%)	629 (13.4%)
Alanine aminotransferase increased	113 (2.4%)	139 (3.0%)
Aspartate aminotransferase increased	91 (2.0%)	112 (2.4%)
Blood alkaline phosphatase increased	36 (0.8%)	57 (1.2%)
Blood lactate dehydrogenase increased	45 (1.0%)	56 (1.2%)
Gamma-glutamyltransferase increased	83 (1.8%)	126 (2.7%)
Haemoglobin decreased	112 (2.4%)	134 (2.9%)
Platelet count increased	40 (0.9%)	50 (1.1%)
Metabolism and nutrition disorders		
Any event	115 (2.5%)	152 (3.2%)
Hypokalaemia	42 (0.9%)	57 (1.2%)
Musculoskeletal and connective tissue disorders		
Any event	287 (6.2%)	263 (5.6%)
Arthralgia	63 (1.4%)	80 (1.7%)
Muscle spasms	54 (1.2%)	32 (0.7%)
Pain in extremity	75 (1.6%)	55 (1.2%)
Nervous system disorders		
Any event	416 (8.9%)	394 (8.4%)
Dizziness	151 (3.2%)	143 (3.0%)
Headache	108 (2.3%)	107 (2.3%)
Syncope	56 (1.2%)	32 (0.7%)
Psychiatric disorders		
Any event	301 (6.5%)	291 (6.2%)
Insomnia	158 (3.4%)	167 (3.6%)
Renal and urinary disorders		
Any event	209 (4.5%)	201 (4.3%)
Urinary retention	84 (1.8%)	84 (1.8%)
Skin and subcutaneous tissue disorders		
Any event	398 (8.5%)	351 (7.5%)
Blister	67 (1.4%)	43 (0.9%)
Pruritus	97 (2.1%)	79 (1.7%)
Rash	50 (1.1%)	48 (1.0%)
Vascular disorders		
Any event	594 (12.8%)	773 (16.5%)
Deep vein thrombosis	198 (4.3%)	363 (7.7%)
Haematoma	50 (1.1%)	59 (1.3%)
Hypertension	56 (1.2%)	67 (1.4%)
Hypotension	218 (4.7%)	215 (4.6%)
Wound haemorrhage	48 (1.0%)	44 (0.9%)

Incidence = number of events / number at risk, where: number of events = number of subjects reporting the event; number at risk = number of subjects in reference population. Only treatment-emergent adverse events which occurred up to 2 days after the last dose of study medication are included. Note: The table presents MedDRA terms of the primary pathology, sorted first by Primary System Organ Class (alphabetical order) then by Preferred Term (alphabetical order) Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term

- Serious adverse events/deaths/other significant events

Deaths
No death occurred in phase I clinical trials. Out of 2232 randomized subjects in the phase II VTE prevention studies, seven cases of death were reported in the rivaroxaban treatment group. No deaths were reported in the subjects receiving enoxaparin. For five out of seven fatal cases the onset of the critical event leading to death occurred after the end of treatment. In the treatment group of 2.5 mg bid, which was the lowest dose tested in phase II studies, there were three reports of death, two of them in subjects with pulmonary embolism and one in a subject with symptoms possibly related to pulmonary embolism. Events leading to death in the remaining dose groups were infections, cardio-respiratory arrest and pulmonary embolism. None of the reported fatal cases were believed to be related to bleeding events.

In phase III trials, eight deaths were recorded among the subjects from the rivaroxaban treatment groups and nineteen subjects from the enoxaparin/placebo treatment groups. From the eight subjects of the rivaroxaban treatment group two did not receive active study medication. From the reported events after start of active study medication until the end of the follow-up period, the most frequent cause of death in the rivaroxaban and enoxaparin group was pulmonary embolism or suspected pulmonary embolism (2 *vs* 6), followed by respiratory failure (2 *vs* 4) and myocardial infarction/cardiac arrest (0 *vs* 4). In summary, the death numbers were numerically lower in the rivaroxaban treatment group compared to the enoxaparin treatment group (pooled data irrespective of treatment duration). In the three controlled clinical studies there was no report of fatal bleeding or intracranial bleeding during the treatment with active study medication.

Non fatal serious adverse events
In the phase I clinical pharmacological trials eight out of 1260 subjects who were evaluated in safety data analysis reported serious adverse events. None of these events was considered to be related to rivaroxaban and no safety signal was derived from these events.

In phase II studies treatment-emergent serious adverse events and drug-related serious adverse events were not different between the treatment groups of the subjects enrolled in VTE prevention studies. The most frequently reported treatment-emergent serious adverse event was DVT (2% in the rivaroxaban treatment group *vs* 6% in the enoxaparin treatment group).

During the 2 week treatment, the incidence of serious treatment-emergent adverse events reported by subjects valid for safety analysis in the 3 phase III studies during the entire treatment period or until day 12 ± 2 was similar in both treatment groups. Differences between the treatment groups did not exceed 1% with exception of DVT. The investigator reported DVT rate was lower in rivaroxaban-treated subjects in both analyses (0.6% in the rivaroxaban treatment group *vs* 1.9% in the enoxaparin/placebo treatment group for all three studies irrespective of treatment duration). The most frequent serious treatment-emergent adverse events in both treatment groups during both treatment periods were procedural complications, such as joint dislocation and dislocation of joint prosthesis and vascular disorders, in particular DVTs .

The incidence rates of serious treatment-emergent, drug-related adverse events for the 5-week treatment in the RECORD 1 study were 1.2% (26/2209) in the rivaroxaban treatment group *vs* 1.0% (23/2224) in the enoxaparin treatment group. These were 1.1% (13/1228) in the rivaroxaban treatment group *vs* 1.4% (17/1229) in the enoxaparin/placebo treatment group in study RECORD 2.

The incidence of serious treatment-emergent, drug-related adverse events reported in the safety population of the 3 pivotal phase III studies during the entire treatment period or until day 12 ± 2 and until day>35 was comparable in both treatment groups. The most frequently reported serious treatment-emergent, drug-related adverse events in both treatment groups during both treatment periods were gastrointestinal disorders, general disorders, increased ALT, injury, poisoning, and procedural complications, operative haemorrhage, and vascular disorders, and haematoma.

Incidence of Serious Treatment-Emergent Adverse Events Coded by MedDRA*

Primary System Organ Class, Preferred Term	Rivaroxaban 10 mg od (N = 4657)	Enoxaparin/ Placebo (N = 4692)
Any system organ class	326 (7.0%)	422 (9.0%)
Cardiac disorders	28 (0.6%)	35 (0.8%)
Gastrointestinal disorders	25 (0.5%)	23 (0.5%)
General disorders and administration site conditions	14 (0.3%)	25 (0.5%)
Infections and infestations	53 (1.1%)	51 (1.1%)
Injury, poisoning, and procedural complications	85 (1.8%)	99 (2.1%)
Dislocation of joint prosthesis	14 (0.3%)	28 (0.6%)
Joint dislocation	11 (0.2%)	24 (0.5%)
Investigations	37 (0.8%)	34 (0.7%)
Respiratory, thoracic, and mediastinal disorders	15 (0.3%)	25 (0.5%)
Vascular disorders	47 (1.0%)	112 (2.4%)
Deep vein thrombosis	29 (0.6%)	91 (1.9%)

Note: Incidence = number of events / number at risk, where: number of events = number of subjects reporting the event; number at risk = number of subjects in reference population
Note: Only treatment-emergent adverse events which occurred up to 2 days after the last dose of study medication are included. Note: The table presents MedDRA terms of the primary pathology, sorted by Primary System Organ Class (alphabetical order) Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities
**(Pooled Data of the 3 Controlled Clinical Studies of Phase III (11354, 11356 and 11357), all Primary System Organ Classes and Preferred Terms with ≥0.5% Incidence)*

Bleedings

All bleeding events were classified into two categories:

- Major bleeding event.
- Non-major bleeding event, including clinically relevant non-major bleeding and other non-major bleeding.

Major bleeding events included:

- Fatal bleeding.
- Bleeding into critical organ (e.g. retroperitoneal, intracranial, intraocular or intraspinal bleeding/haemorrhagic puncture).
- Bleeding requiring re-operation.
- Clinically overt extra-surgical site bleeding associated with ≥2 g/dL fall in hemoglobin.
- Clinically overt extra-surgical site bleeding leading to infusion of ≥2 units of whole blood or packed cells.

Non-major bleeding events were bleeding events that did not fulfil the criteria of major bleeding. This included clinically relevant non-major bleeding events. Clinically relevant non-major bleeding events included multiple source bleeding, spontaneous haematoma >25 cm^2, excessive wound haematoma, spontaneous nose bleeding >5 min, macroscopic haematuria (spontaneous or lasting >24 hours if associated with an intervention), spontaneous rectal bleeding (more than spot on a toilet paper), gingival bleeding >5 min, coughing blood, haematemesis, prolonged bleeding after venipuncture >5 min.

Other clinically relevant non-major bleeding events that were reported but that did not meet the above criteria were classified into the following categories: surgical site bleeding, intra-articular with trauma, events, slightly higher bleeding incidences were observed in the pooled rivaroxaban groups. However, a significant proportion of the patients in the control groups was treated with a placebo for approximately 3 weeks and a more relevant comparison can be made when all phase III patients having active treatment for 35 days are compared.

Bleedings, all patients in the phase III studies having active treatment for 35 days

Endpoint/ components	RECORD 1		RECORD 2
	Rivaroxaban 10 mg od (N=2183) n (%)	Enoxaparin 40 mg od (N=2198) n (%)	Rivaroxaban 10 mg od (N=1228) n (%)
Any bleeding	119 (5.5)	109 (5.0)	82 (6.7)
Any major or non-major clinically relevant bleeding	66 (3.0)	42 (1.9)	42 (3.5)
Major bleeding			
Any event	5 (0.2)	1 (<0.1)	1 (0.1)
Fatal bleeding	0 (0.0)	0 (0.0)	0 (0.0)
Critical bleeding	1 (<0.1)	0 (0.0)	0 (0.0)
Intracranial	0 (0.0)	0 (0.0)	0 (0.0)
Retroperitoneal	0 (0.0)	0 (0.0)	0 (0.0)
Intraspinal	0 (0.0)	0 (0.0)	0 (0.0)
Intraocular	1 (<0.1)	0 (0.0)	0 (0.0)
Clinically overt extra-surgical site bleeding associated with a fall in hemoglobin of ≥2 g/dL	2 (<0.1)	1 (<0.1)	1 (0.1)
Clinically overt extra-surgical site bleeding leading to transfusion of ≥2 units of whole blood or packed cells	2 (<0.1)	1 (<0.1)	1 (0.1)
Bleeding leading to re-operation	2 (<0.1)	0 (0.0)	0 (0.0)
Non-major bleeding			
Any event	114 (5.2)	108 (4.9)	63 (5.1)
Any clinically relevant non-major bleeding	61 (2.8)	41 (1.9)	31 (2.5)

Thus, in adequate head to head comparisons there is a weak trend for a slightly higher rate of bleeding in the rivaroxaban treated groups. However, there are no differences in fatal bleedings or bleedings into critical organs. The distribution of bleeding locations and of bleeding severity seems to be similar between the treatment groups.

There have been no reports of accidental or intentional overdose with rivaroxaban, however, there is a potential for increased bleeding related to overdose. No specific antidote is known and the SPC recommends the several steps to help manage events of haemorrhage. This includes the use of pro-coagulants, such us the activated prothrombin complex concentrate, prothrombin complex concentrate, recombinant factor VIIa. There is, however, no experience in the use of these substances in subjects treated with rivaroxaban; only non clinical data are available. Formal clinical investigations to demonstrate the effectiveness of the existing pro-coagulatory drugs in the settings of severe bleeding and/or rivaroxaban overdose is not feasible and might be unethical. Thus, the experience from the future occasional events of administration of pro-coagulants in relevant cases of drug overdose in the post-marketing use will be monitored and reported to the CHMP in Periodic Safety Update Reports.

Cardiovascular events

During active treatment 11 subjects of the rivaroxaban 10 mg od treatment group *vs* 16 subjects of the enoxaparin 40 mg od treatment group had cardiovascular events adjudicated as stroke, myocardial infarction and cardiovascular death. After discontinuation of the active treatment and during follow-up the respective numbers were 11 *vs* 7. In general, the cardiovascular events adjudicated as stroke, myocardial infarction and cardiovascular death were evenly distributed between the treatment groups during the entire observation period.

No QTc prolonging effect was observed for rivaroxaban in elderly male and female subjects in a dedicated QT study, which was a four way crossover study, that tested two doses of rivaroxaban (15 and 45 mg) as well as placebo and moxifloxacin (400 mg) as a positive control in 54 healthy male and female volunteers older than 50 years. No meaningful differences in ECG recordings or arrhythmias between the treatment groups were noted in the phase II programme.

The type and duration of surgery and of anaesthesia as well as time to mobilization were recorded in subjects valid for safety analysis. There was no noticeable difference between the rivaroxaban and enoxaparin/placebo treatment groups in any of these parameters or in the vital parameters or in blood pressure or heart rate.

There was a difference in non-infectious wound complications 188 (4.1%) *vs* 133 (2.9%) in the rivaroxaban *vs* enoxaparin groups, respectively. A difference was also noted for wound secretion. There was, however, no difference between the treatment groups for serious non-infectious wound complications. Following the data re-analysis, the statistical significance of these observations remains valid; however, there are no obvious differences with regard to severe complications.

- Laboratory findings

Extensive clinical laboratory evaluations were performed in the 3 phase III studies and included:

- Haematology: haematocrit, haemoglobin, RBC, WBC, differential blood count, and platelets
- Blood chemistry: glucose, calcium, sodium, potassium, creatinine, urea, uric acid, albumin, ALT, AST, GGT, LDH, alkaline phosphatase, bilirubin (total, direct, and indirect), amylase, and lipase

Overall, the incidence rates of laboratory abnormalities in the rivaroxaban and enoxaparin treatment groups were similar.

The imbalance in the incidences of the creatinine and urea levels above upper limit of normal (ULN) was apparent. The levels of creatinine were increased on 8.54% of subjects in the rivaroxaban group *vs* 6.59% in the comparator group. Similarly, 8.55% of patients treated with rivaroxaban had increased values of urea as compared with 6.41% of patients treated with the comparator. Indeed, further examination of the available data confirmed that mild or moderate elevations of serum creatinine are slightly more common amongst the rivaroxaban treated patients as compared to the enoxaparin treated patients. There seems to be no further increase after 2 weeks of treatment. However, the observed increase could implicate an increased risk for clinically relevant impairment of renal function in susceptible patients although such events could be so rare that they are not easily detected. The extensive analyses of the pattern of creatinine laboratory derangements do not indicate any clinically relevant differences between the treatment groups in the hip studies. In addition, there is no clear signal that patients with elevations at baseline or early in the treatment period would deteriorate with further increase in the pooled analyses of the hip studies RECORD 1 and RECORD 2 with up to 5 weeks treatment. Patients in study 3 were older and had a higher incidence of elevated creatinine values at baseline. Further analyses on the pivotal clinical studies regarding these aspects will probably not bring any additional benefit. However, the safety concern cannot be neglected based on these analyses and it will be important to follow any clinically relevant renal adverse events through routine pharmacovigilance and in the planned post-marketing study, and to be reported in the future Periodic Safety Update Reports (PSURs).

Potential abnormalities of liver function tests were intensively monitored and occurred with a comparable or lower incidence in rivaroxaban *vs* enoxaparin treated subjects. In terms of elevations for all predefined ALT thresholds (ALT> 1.5x ULN, ALT> 2 x , ALT> 3x ULN, ALT > 5 x ULN, ALT > 8 x ULN, ALT > 10 x ULN and ALT > 20 x ULN) numerically lower frequencies were observed in rivaroxaban treated subjects as compared to enoxaparin treated subjects. Most of the ALT elevations are seen after surgery. ALT was used as a marker of hepatocellular injury as elevated levels are rather sensitive for toxic effects at the level of liver cell membrane. However, these events are not specific for e.g. toxic drug effects. Overall from the data no clear evidence could be provided that might indicate a significant difference with regard to hepatotoxicity for rivaroxaban compared with enoxaparin. Nevertheless, in order to detect rare serious events surveillance of hepatic adverse events should be included in the future PSURs and in the planned post-marketing study.

The non clinical studies in rats and dogs might indicate some signal concerning a pancreatic toxicity (please see section Toxicology). Rivaroxaban seems to be highly distributed in the pancreas and thus, the potential pancreas enzyme abnormalities that could be observed during the clinical study program

were of interest. Lipase and amylase elevations were seen only in a small number of patients included in the phase II and III programme. However, the rare cases of elevated enzyme levels, in some cases connected with abdominal complaints, did not provide the evidence for an association between upper abdominal pain and laboratory values indicating pancreatitis. Furthermore, in the patients included in the phase III trials non drug related causes for pancreatitis are also probable and could not be excluded.

There were no relevant differences between both treatment groups in terms of bilirubin abnormalities.

- Safety in special populations

For the category of treatment-emergent major or non-major bleeding events, the subgroup analysis showed a trend towards higher bleeding event rates for subjects with a BMI<18.5, subjects with decreased (<50 kg) or increased (>110 kg) body weight in the rivaroxaban group when compared with the enoxaparin group. Subjects older than 75 years and fragile subjects showed tendency towards a lower risk for bleeding events in rivaroxaban treated subjects compared to enoxaparin treated subjects. However, these trends are based on overall low event rates in both treatment groups.

Men had higher bleeding events rates of treatment-emergent major or non-major bleeding events compared to women, and had higher bleeding rates when treated with rivaroxaban compared to enoxaparin.

There was no clinically relevant difference in the incidence and pattern of treatment-emergent adverse events between the two treatment groups within any of the four different race strata.

Overall, considering the presented subgroup analyses of bleeding events in the three phase III trials and the relevant data available for the comparator, there is no suggestion of the need to restrict the use of rivaroxaban according to gender, race, age or bodyweight.

Patients with hepatic impairment
Patients with significant liver disease (cirrhosis, acute clinical or chronic active hepatitis) were excluded in from study participation in the RECORD studies as per exclusion criteria. However, data are available from patients with pre-operative elevated ALT and/or elevated bilirubin values.

The PK/PD changes in these subjects are markers for the severity of the underlying hepatic disease which is expected to lead to a subsequent increased bleeding risk in this subject group. There are appropriate safety warnings adequately included in the SPC and further analysis of clinical data revealed only a slight numerical difference between the treatment groups for the elevations of hepatic enzymes in the patients with a history of hepatic disease. These differences are small and in most cases transient of a non-progressive nature. Thus, rivaroxaban is contraindicated in patients with hepatic disease which is associated with coagulopathy and a clinically relevant bleeding risk. Furthermore, due to the fact that rivaroxaban exposure was increased 2.3 fold in cirrhotic patients with moderate hepatic impairment (classified as Child Pugh B) and there may be patients with moderate hepatic impairment but without coagulopathy, these would not be covered by the contraindication. Rivaroxaban may be used with caution in cirrhotic patients with moderate hepatic impairment (Child Pugh B) if it is not associated with coagulopathy. The SPC reflects this information.

Patients with renal impairment
Rivaroxaban is eliminated by both metabolic degradation and direct renal excretion of unchanged active compound. Thus, renal impairment is important for the safety of this product.
Results of the phase I studies indicate an increase in rivaroxaban exposure correlating to the decrease in renal function, as assessed *via* creatinine clearance measurements. The studies conducted in VTE prevention with rivaroxaban 10 mg od restricted inclusion of subjects by renal function due to the contraindications for enoxaparin. The phase III safety population of 4657 subjects treated with rivaroxaban included 25 subjects (0.5%) with a calculated creatinine clearance of < 30 ml/min and 298 (6%) of subjects with a calculated creatinine clearance between 30 and 50 mL/min. A higher number of bleeding events was seen in subjects with severe renal impairment (< 30 ml/min). However, the safety evaluation did not reveal any tendency for increased risk of bleeding in patients with CLcr 30-

40 ml/min. Although the number of patients is fairly low, the PK data suggests only a modest increase in exposure in these patients. Patients with severe renal impairment were excluded from the phase III studies and the available PK data indicate a modest increase in exposure in severe renal impairment. Patients with CLcr <15 ml/min have not been studied. Higher exposure to the active substance might be expected in these patients. In summary, the SPC does not recommend the use of rivaroxaban in patients with creatinine clearance <15 ml/min. The medicinal product is to be used with caution in patients with severe renal impairment and also in patients with moderate renal impairment concomitantly receiving other medication increasing rivaroxaban plasma concentrations.

- Safety related to drug-drug interactions and other interactions

Clinically relevant drug-drug interactions with substrates of CYP isozymes due to rivaroxaban co-medication are rather unlikely, as no significant influence of rivaroxaban on biotransformation reactions catalyzed by relevant cytochrome P450 isoforms was observed. The likelihood to observe clinically relevant drug-drug interactions through induction of CYP1A2, 3A4, 2B6 or 2C19 is considered to be very low.

To confirm the absence of any interaction potential by rivaroxaban co-medication specific *in vivo* drug-drug interaction studies were conducted with CYP3A4/ CYP2C9/P-gp substrates (midazolam, digoxin, atorvastatin, warfarin) and the lack of interaction potential caused by rivaroxaban as co-medication could be demonstrated in all cases.

The use of rivaroxaban is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics such as ketoconazole, itraconazole, voriconazole and posaconazole or the HIV protease inhibitors, since these medicinal products have a significant impact on rivaroxaban disposition. This is adequately reflected in the product SPC.

During the concomitant use of nonsteroidal anti-inflammatory drug (NSAID), opioids, statins, nitrates, platelet aggregation inhibitors or acetylic salicylic acid, no increase in the bleeding risk beyond that seen with enoxaparin was observed in the phase III studies. However, care must be taken when co-administering rivaroxaban and other anti-coagulants due to the possible increase of bleeding.

- Discontinuation due to adverse events

The total number of adverse events resulting in treatment discontinuation was higher in the pooled active comparator study arms. This was evident for all most frequently occurring events leading to discontinuation, i.e. vascular disorders, respiratory, thoracic, and mediastinal disorders, injuries, poisoning, and procedural complications, gastrointestinal disorders and cardiac disorders. The pattern of adverse events leading to discontinuation in the rivaroxaban groups does not implicate any specific safety concerns.

During the phase III studies discontinuation rates for any reason from all randomised subjects were similar with 10.9% in the rivaroxaban treatment group and 12.1% in the enoxaparin/placebo treatment group. The same situation was seen for the discontinuation rates due to adverse events, which were 3.1% in the rivaroxaban treatment group and 4.0% in the enoxaparin treatment group until day 12 ± 2 and 3.8% in the rivaroxaban treatment group *vs* 4.5% in the enoxaparin treatment group with the extended 5-week treatment period. The most frequently reported events in the rivaroxaban *vs* enoxaparin group with an incidence ≥ 0.2% were atrial fibrillation (0.1% *vs* 0.2%), nausea (0.2% *vs* 0.3%), PE (0.2% *vs* 0.3%) and DVT (0.1% *vs* 0.4%). From the preferred terms with an incidence ≥ 0.2% the data indicated a difference between the treatment groups for DVT. Overall, these data show that the discontinuation rates due to adverse events during extended treatment (5-week treatment) are low and comparable between rivaroxaban and enoxaparin treatment and do not seem to contribute significantly to rivaroxaban discontinuation.

- Post marketing experience

There is currently no post-marketing experience with the use of this fixed dose combination.

2.5 Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan.

Table Summary of the risk management plan

Safety concern	**Proposed pharmacovigilance activities (routine and additional)**	**Proposed risk minimisation activities (routine and additional)**
Important identified Risks		
Haemorrhage	Routine pharmacovigilance activities Additional information from ongoing trials Additional information from the post-marketing observational study (XAMOS) in 15000 patients and drug utilisation database study/studies	Contraindication in SmPC section 4.3 “Contraindication” "Clinically significant active bleeding. Hepatic disease associated with coagulopathy and clinically relevant bleeding risk (see section 5.2)." Warning in SmPC section 4.4 “Special warnings and precautions for use”*"Haemorrhagic risk* "Several sub-groups of patients, as detailed below, are at increased risk of bleeding. These patients are to be carefully monitored for signs of bleeding complications after initiation of treatment. This may be done by regular physical examination of the patients, close observation of the surgical wound drainage and periodic measurements of haemoglobin. Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site." Warning in SmPC section 4.5 “Interaction with other medicinal products and other forms of interactions” *"CYP3A4 and P-gp inhibitors* Co-administration of rivaroxaban with ketoconazole (400 mg once a day [od]) or ritonavir (600 mg twice a day [bid]) led to a 2.6 fold / 2.5 fold increase in mean rivaroxaban AUC and a 1.7 fold / 1.6 fold increase in mean rivaroxaban Cmax, with significant increases in pharmacodynamic effects which may lead to an increased bleeding risk. Therefore, the use of Xarelto is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics such as ketoconazole, itraconazole, voriconazole and posaconazole or HIV protease inhibitors. These active substances are strong inhibitors of both CYP3A4 and P-gp (see section 4.4). Fluconazole is expected to have less effect on rivaroxaban exposure and can be co-administered with caution. *Anticoagulants* After combined administration of enoxaparin (40 mg single dose) with rivaroxaban (10 mg single dose) an additive effect on anti-Factor Xa activity was observed without any additional effects on clotting tests (PT, aPTT). Enoxaparin did not affect the pharmacokinetics of rivaroxaban. Due to the increased bleeding risk care is to be taken if patients are treated concomitantly with any other anticoagulants (see section

		4.4). *NSAIDs/platelet aggregation inhibitors* No clinically relevant prolongation of bleeding time was observed after concomitant administration of rivaroxaban and 500 mg naproxen. Nevertheless, there may be individuals with a more pronounced pharmacodynamic response. No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with 500 mg acetylsalicylic acid. Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) did not show a pharmacokinetic interaction but a relevant increase in bleeding time was observed in a subset of patients which was not correlated to platelet aggregation, P-selectin or GPIIb/IIIa receptor levels. Care is to be taken if patients are treated concomitantly with NSAIDs (including acetylsalicylic acid) and platelet aggregation inhibitors because these medicinal products typically increase the bleeding risk (see section 4.4)." Haemorrhage is listed in section 4.8 of the SPC
Important Potential Risks		
Increase in LFTs, bilirubin	Routine pharmacovigilance activities Additional information from ongoing trials	Elevated liver enzymes /bilirubin are listed in section 4.8 of the SPC
Transient increase of lipase and amylase	Routine pharmacovigilance activities Additional information from ongoing trials	Increase lipase and amylase are listed in section 4.8 of the SPC
Renal impairment – increase in creatinine	Routine pharmacovigilance activities Additional information from ongoing trials Additional information from the post-marketing observational study (XAMOS) in 15000 patients	Renal impairment is listed in section 4.8 of the SPC
Important missing information		
Patients undergoing major orthopaedic surgery other	Routine pharmacovigilance activities Additional information from drug utilization	SmPC Section 4.1 “Therapeutic indications” "Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery."

than elective hip or knee replacement surgery	study/studies	SmPC Section 4.4 “Special warnings and precautions for use” *"Hip fracture surgery* Rivaroxaban has not been studied in clinical trials in patients undergoing hip fracture surgery to evaluate efficacy and safety in these patients. Therefore, rivaroxaban is not recommended in these patients."
Patients with severe renal impairment (CrCl < 30ml/min)	Routine pharmacovigilance activities Additional information from the post-marketing observational study (XAMOS) in 15000 patients	SmPC Section 4.2 “Posology and method of administration” – renal impairment *"Renal impairment* No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50 - 80 ml/min) or moderate renal impairment (creatinine clearance 30 - 49 ml/min) (see section 5.2). Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased in this patient population, therefore, Xarelto is to be used with caution in these patients. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.4 and 5.2)." Warning in SmPC Section 4.4 “Special warnings and precautions for use” *"Renal impairment* *In patients with severe renal impairment (creatinine clearance < 30 ml/min) rivaroxaban plasma levels may be significantly increased which may lead to an increased bleeding risk. Use is not recommended in patients with creatinine clearance < 15 ml/min. Xarelto is to be used with caution in patients with creatinine clearance 15 - 29 ml/min (see sections 4.2 and 5.2).* *Xarelto is to be used with caution in patients with moderate renal impairment (creatinine clearance 30 - 49 ml/min) concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations (see section 4.5)."*
Remedial pro-coagulant therapy for excessive haemorrhage	Routine pharmacovigilance activities Additional information from ongoing trials Additional information from the post-marketing observational study (XAMOS) in 15000 patients	SmPC Section 4.9 “Overdose” *"Overdose following administration of rivaroxaban may lead to haemorrhagic complications due to its pharmacodynamic properties.* *A specific antidote antagonising the pharmacodynamic effect of rivaroxaban is not available.* *The use of activated charcoal to reduce absorption in case of rivaroxaban overdose may be considered.* *Should bleeding occur, management of the haemorrhage may include the following steps:* • *delay of next rivaroxaban administration or discontinuation of treatment as appropriate. Rivaroxaban has mean terminal half-lives between 7 and 11 hours (see section 5.2).* • *appropriate symptomatic treatment, e.g. mechanical compression, surgical interventions, fluid replacement and haemodynamic support, blood product or component transfusion should be considered.*

		If life-threatening bleeding cannot be controlled by the above measures, administration of one of the following procoagulants may be considered: • *activated prothrombin complex concentrate (APCC)* • *prothrombin complex concentrate (PCC)* • *recombinant factor VIIa.* *However, there is currently no experience with the use of these medicinal products in individuals receiving rivaroxaban. The recommendations are based on limited non-clinical data. Re-dosing of these procoagulants shall be considered and titrated depending on improvement of bleeding."*
Patients receiving systemic treatment with Cyp3A4 and P-gp inhibitors other than azole-antimycotics (e.g. ketoconazole) and HIV protease inhibitors (e.g. ritonavir)	Routine pharmacovigilance activities Additional information from the post-marketing observational study (XAMOS) in 15000 patients and drug utilisation database study/studies	SmPC Section 4.5 "Interaction with other medicinal products and other forms of interaction" *"CYP3A4 and P gp inhibitors* *[...] Fluconazole is expected to have less effect on rivaroxaban exposure and can be co-administered with caution.* *Active substances strongly inhibiting only one of the rivaroxaban elimination pathways, either CYP3A4 or P gp, are expected to increase rivaroxaban plasma concentrations to a lesser extent. Clarithromycin (500 mg bid), for instance, considered as strong CYP3A4 inhibitor and moderate P gp inhibitor, led to a 1.5 fold increase in mean rivaroxaban AUC and a 1.4 fold increase in Cmax. This increase is not considered clinically relevant.* *Erythromycin (500 mg three times a day [tid]), which inhibits CYP3A4 and P gp moderately, led to a 1.3 fold increase in mean rivaroxaban AUC and Cmax. This increase is not considered clinically relevant."*
Pregnant or breast-feeding women	Routine pharmacovigilance activities Additional information from drug utilisation database study/studies	SmPC Section 4.3 "Contraindication" "Pregnancy and lactation (see section 4.6)." SmPC Section 4.6 "Pregnancy and lactation" *"Pregnancy* There are no adequate data from the use of rivaroxaban in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, Xarelto is contraindicated during pregnancy (see section 4.3). Women of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban. *Lactation* No data on the use of rivaroxaban in breast-feeding women are available. Data from animals indicate that rivaroxaban is secreted into milk. Therefore Xarelto is contraindicated during breast-feeding (see section 4.3). A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from therapy."

2.6 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

Non-clinical pharmacology and toxicology

The non clinical pharmacological programme provided a good characterisation of the pharmacological properties of rivaroxaban. Pharmacodynamic receptor binding and enzyme inhibition investigations adequately demonstrate that rivaroxaban is a selective FXa inhibitor and that pharmacological effects due to interaction with unrelated receptors or enzymes are unlikely.

Inhibition of FXa leads to secondary changes in coagulation parameters such as aPTT and PT. Efficacy was demonstrated in various thrombotic models and in general there appears to be a dose margin between the antithrombotic effect and the risk for increased bleeding. Safety pharmacology studies do not suggest any acute adverse exaggerated pharmacological effects of rivaroxaban, except bleeding and this was confirmed in the clinical environment.

Rivaroxaban has a structural similarity to the antibiotic linezolid and therefore might exhibit a potential for inhibition of the bacterial protein synthesis. An additional, related, concern is the possibility of mitochondrial toxicity, since linezolid is known to inhibit mitochondrial protein synthesis leading to a loss of mitochondrial function. No antibacterial activity was shown for rivaroxaban , however, the potential risk for mitochondrial toxicity is not ruled out. This does not represent a considerable risk for the approved short-term indication. In order to provide further clarifications, mitochondrial toxicity of rivaroxaban is planned to be addressed in further nonclinical investigation, which is particularly relevant in case of considering an extension to long-term treatment in the future.

The drug interaction investigations did not indicate any specific concerns. Some additive effects on bleeding were observed in concomitant administration of rivaroxaban with antihaemostatic drugs. There is a potential for the recombinant factor VII to serve as rivaroxaban antidotes, but this has not been confirmed in clinical settings.

The pharmacokinetic and metabolic profile of rivaroxaban are well characterised.

The increased incidence of pancreatic lesions in animals and adverse effects on liver, including changes of hepatic enzyme and bilirubin levels and incidence of liver necrosis, observed in non clinical studies are thought to be found in the human trials, e.g. increased lipase, amylase and hepatic enzyme levels. Furthermore, some teratogenic effects were seen at clinically relevant exposure affecting mainly skeleton, heart and vessels. In addition, true placenta and teratogenic effects of rivaroxaban cannot be excluded. Reduced viability of the offsprings was observed at the doses that were toxic to dams. Pregnancy and breastfeeding during rivaroxaban administration are contraindicated. The relevant information on placental toxicity, embryofoetal toxicity and teratogenicity are included in the SPC.

The environmental risk of rivaroxaban was assessed and the CHMP concluded that there is no need for a phase II assessment in frame of the currently planned use of rivaroxaban.

Clinical pharmacology

Rivaroxaban has a favourable pharmacokinetic profile with several elimination pathways (about 36% renal excretion, 32% CYP-mediated metabolism and 14% hydrolysis) and a fairly small risk for major increases in exposure. Rivaroxaban exposure is increased to a significant extent in patients with moderate hepatic impairment and in patients receiving concomitant medication with dual inhibitors of CYP3A4 and P-gp. Data are lacking in patients with hepatic impairment associated with impaired haemostasis and in end stage renal disease patients (creatinine clearance <15 ml/min). Appropriate

warnings and recommendations have been included in the SPC for patients at risk for increased exposure. The applicant has ongoing activities to further investigate the possibility to develop a laboratory test that could be used for monitoring patients at increased risk for bleeding.

Efficacy

The dose finding, phase II studies in VTE prevention setting were performed with the doses ranging from 2.5 mg bid to 30 mg bid and a with the doses range from 5 mg od to 40 mg od. Data indicated a target therapeutic window of 5 mg to 20 mg total daily dose in the prevention of VTE after major orthopedic surgery. Total daily doses of 20 mg and beyond were associated with a higher incidence of bleeding events and there was only an evidence for small differences in efficacy between the 5 mg bid and the 10 mg od dosing regimens. Higher compliance to treatment a possible better safety profile of the 10 mg od dosing regimen in comparison with the 5 mg bid regimen can be expected. Further investigations confirmed that the optimal net clinical benefit (avoidance of major VTE and/or major bleeding) was observed in the 10 mg od dose. The use of the once-daily dose of 10 mg was thus adequately justified and was selected for investigations in phase III studies in the VTE prevention indication.

The pivotal phase III studies had a conventional design for new agents within this therapeutic area. Two independent comparative studies, one in hip surgery and one in knee surgery have been performed. The study populations were representative of a target population undergoing elective major orthopaedic surgery of the lower limbs. The rivaroxaban regimens were superior to the well established enoxaparin regimens with regard to the composite primary efficacy parameter (venographically detected total VTEs, symptomatic VTEs and death) and the results were supported by different sensitivity analyses. Superiority was also demonstrated for a more stringent endpoint of major VTEs consistent with the CHMP guidance recommendations, excluding asymptomatic distal VTEs). As expected, the rates of symptomatic VTE events were low and these results were consistent with the primary efficacy results.

A supportive study comparing a 5 week prophylactic rivaroxaban regimen with a conventional 2 week enoxaparin regimen in elective hip surgery demonstrated superiority of the rivaroxaban regimen.

Hip fracture patients were not included in the clinical study programme. The proposed indication was therefore found to be not acceptable by the CHMP. It is expected that rivaroxaban would be effective in the hip fracture surgery. There are higher VTE rates in hip fracture surgery as compared to the elective hip surgery. Marked differences in the overall mortality rates with higher mortality among the fracture patients and a clear tendency to the higher incidence of fatal PEs are also relevant for this patient population. As a group, fracture patients are of advanced age and more fragile, and have a larger risk of concomitant diseases. Rivaroxaban represents a fairly new pharmacological concept and some uncertainties with regard to the safety of the drug when used in the routine clinical setting remain. Specific controlled efficacy and safety data from patients with hip fracture were not available. Given the different risk profile for these patients, the current indication of rivaroxaban was restricted by the CHMP to adult patients undergoing elective hip or knee replacement surgery. Rivaroxaban is not recommended for use in patients undergoing hip fracture surgery.

Safety

The safety profile of rivaroxaban in the proposed dose for up to 5 weeks treatment has been well characterised and no major safety concerns have been identified so far. A relatively large number of subjects were exposed to rivaroxaban. Safety population in phase III studies comprises 4657 subjects randomized to rivaroxaban and 4692 subjects randomized to enoxaparin. Since the product is currently proposed for an exposure not longer than 35 days, safety data with regard to long-term exposure is limited. Only limited data concerning the exposure of >35±4 days is available at this time point, however, no different safety profile became obvious during assessment of this data in comparison to short term treatment (<35±4 days).

Safety aspects such as bleeding events, cardiovascular events and liver enzyme elevations were analysed and assessed. The main safety endpoint during phase II and III studies was the incidence of treatment emergent major bleeding observed not later than 2 days after last intake of study drug.

The most frequently reported treatment-emergent adverse events in phase III controlled clinical studies in both treatment groups during both treatment periods were gastrointestinal disorders, in particular nausea, vomiting, and constipation; general disorders, in particular pyrexia; procedural complications such as postoperative anaemia and procedural pain. The most frequently reported serious treatment-emergent, drug-related adverse events in both treatment groups during both treatment periods were increased ALT, operative haemorrhage, vascular disorders, and haematoma. No differences of relevance concerning type of adverse events between all phases of the clinical trial program became obvious.

Similar rates and profiles of discontinuation of treatment because of adverse events between rivaroxaban treatment and treatment with the comparator enoxaparin were observed. Overall death rate was within the range expected from literature and no specific safety signal could be identified form the assessment of deaths in this application. Haemorrhage (surgical and extra-surgical site haemorrhages) is considered an identified risk. The incidence rate of major bleeding was comparable between the two treatment groups, but the bleeding overall events were numerically higher in the rivaroxaban group in comparison to enoxaparin. The potential for increased bleeding risk for rivaroxaban still exists, especially in cases of incidental overdose or inappropriate off-label use. Such issues are addressed in the Risk Management Plan. There is a trend towards higher bleeding event rates for subjects outside of normal body weight range when compared with enoxaparin treatment. Elderly (> 75 years) and fragile subjects tended to have a lower risk for bleeding events with rivaroxaban, but in both cases, the observations are based on overall low event rates and no dose adjustment was needed. At present no specific antidote is available for rivaroxaban.

Overall from the presented subgroups analyses of bleeding events in the three phase III trials, no evidence was found, to restrict the use of rivaroxaban 10 mg od according to gender, age and bodyweight.

In patients with different stages of renal impairment an increase in rivaroxaban exposure correlating to the decrease in renal function was observed. Furthermore, a higher number of bleeding events was seen in subjects with severe renal impairment. Therefore, as advised in the SPC, rivaroxaban is not to be used in patients with creatinine clearance <15 ml/min and must be used with caution in patients with severe renal impairment as well as in patients with moderate renal impairment concomitantly receiving other medication increasing rivaroxaban plasma concentrations.

No specific safety signal concerning cardiovascular safety was derived from the clinical data.

In order to avoid a potential increase in the pharmacodynamic effect, rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and a clinically relevant bleeding risk. Caution is advised in patients with other hepatic disease of moderate grade. Safety recommendations with regard to patients with hepatic impairment are reflected in the SPC. The use of rivaroxaban in cirrhotic subjects with moderate hepatic impairment resulted in an increased drug exposure in comparison with healthy volunteers.

Observations of transient increases of serum ALT, AST, and bilirubin as well as increases in serum lipase and amylase in patients undergoing major orthopaedic surgery are reflected in the adverse reaction section of the SPC. In most cases, these were asymptomatic elevations. Single cases of symptomatic liver impairment and non-serious pancreatitis have been reported in the clinical studies. There is, however, no clear evidence that rivaroxaban was the causative agent in these cases.

Rivaroxaban is not recommended for treatment of patients receiving concomitant systemic treatment with azole-antimycotics such as ketoconazole, itraconazole, voriconazole and posaconazole or the HIV protease inhibitors due to their interactions with cytochrome P450 and P-gp resulting in a potential to increase bleeding risk. Furthermore, care must be taken when co-administering rivaroxaban and other anti-coagulants due to the possible increase of bleeding.

From the safety database adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics[0] based on a pre-defined algorithm.

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these concerns.

- User consultation

User testing of the Package Leaflet was performed in August and September 2007 in English. Following a pilot round the Package Leaflet was tested in two test rounds, with a total of 20 test persons (healthy volunteers and orthopaedic surgery patients with even distribution of gender, age 50-79). The questionnaire covered the key safety issues of the PL. The methodology followed the Readability guideline. The PL was revised following a pilot round as well as the test rounds 1 and 2. Considering the overall results of the two rounds the result is in line with the requirements.

In conclusion, the user testing is judged acceptable.

Risk-benefit assessment

Based on the outcome of the clinical development programme and the reduced occurrence of thromboembolic events in subjects treated with rivaroxaban, the number of patients in need of therapeutic anticoagulant treatment in the target population may be reduced by approximately 50% when compared to the approved enoxaparin regimen. Considering the risks and practical difficulties with such treatment, this reduction is considered to be beneficial. There is a potential for rivaroxaban to further contribute to the reduction of venous thromboembolism related complications. It is important to note that hip fracture patients were not included in the clinical study programme and this is reflected in the wording of the amended, restricted indication and appropriately addressed in the SPC.

Structural similarity of rivaroxaban with linezolid have raised a concern regarding potential mitochondrial toxicity of rivaroxaban. Although non-clinical studies cannot completely rule out a potential for risk for mitochondrial damage of rivaroxaban, *in vitro*-studies addressing mitochondrial protein synthesis showed that the potential for mitochondrial toxicity might be low and thus not expected to be of concern for the currently approved short-term treatment with rivaroxaban. However, any mitochondrial toxicity is of greater concern if the product is to be used long-term. Therefore, due to limitations of the *in vitro* study, this issue will be explored further in nonclinical setting specifically addressing mitochondrial toxicity.

Rivaroxaban exposure is increased to a significant extent in patients with moderate hepatic impairment and in patients receiving concomitant medication with dual inhibitors of CYP3A4 and P-gp. Data are not available from patients with hepatic impairment associated with impaired haemostasis and in end stage renal disease patients (creatinine clearance <15 ml/min). There are, however, proposed activities to further investigate the possibility to develop a laboratory test that could be used in routine clinical setting for monitoring patients at increased risk for bleeding. The results from these activities will be provided to the CHMP in frame of a follow-up measure. If possible, appropriate recommendations in the SPC including methodology for monitoring patients at increased risk for bleeding might be needed.
No major safety concerns have been identified. Prophylaxis with rivaroxaban might be associated with a slightly higher bleeding tendency than the approved enoxaparin regimen but no major differences are apparent at this point in time. The number of serious bleedings did not differ substantially between the treatment groups in the clinical studies. No clear signals for hepatic or renal adverse events induced by rivaroxaban have been identified. However, such adverse events will be kept under close surveillance in the post-marketing observational study and in the future Periodic Safety Update Reports.

The benefit/risk balance was considered to be positive by the CHMP. An oral treatment without the need for dose titration or monitoring would represent an important alternative to the conventional subcutaneous prophylactic therapy. It has been demonstrated that rivaroxaban therapy in proposed doses is more effective than the approved enoxaparin regimen possibly at the price of a slightly increased bleeding tendency.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns.

- no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Xarelto in the prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery was favourable and therefore recommended the granting of the marketing authorisation.