22 September 2011
EMA/CHMP/301607/2011
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Xarelto

rivaroxaban

Procedure No.: EMEA/H/C/000944/X/0010

Note

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

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Product information

Name of the medicinal product:	Xarelto
Applicant:	Bayer Pharma AG D-13342 Berlin Germany
Active substance:	rivaroxaban
International Nonproprietary Name/Common Name:	rivaroxaban
Pharmaco-therapeutic group (ATC Code):	Other antithrombotic agents (B01AX06)
Therapeutic indication(s):	Treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT and pulmonary embolism following an acute DVT in adults.
Pharmaceutical form(s):	Film-coated tablet
Strength(s):	15 mg, 20 mg
Route(s) of administration:	Oral use
Packaging:	blister (PP/alu)
Package size(s):	10 x 1 tablet, 100 x 1 tablet, 14 tablets, 28 tablets, 42 tablets, 98 tablets

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant Bayer Schering Pharma AG submitted on 24 November 2010 an extension application for Marketing Authorisation to the European Medicines Agency (EMA) for Xarelto, through the centralised procedure pursuant to article 19 of Commission Regulation (EC) No 1234/2008 and Annex I (point 2. (c) addition of a new strength).

The applicant applied for the following indication:

Treatment of deep vein thrombosis (DVT), and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/95/2010 on the agreement of a paediatric investigation plan (PIP), including a waiver.

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Not applicable.

Market Exclusivity

Not applicable.

Scientific Advice:

The applicant received Scientific Advice from the CHMP in 2006. The Scientific Advice pertained to clinical aspects of the dossier.

Licensing status

Xarelto has been given a Marketing Authorisation in EU on 30 September 2008.

1.2. Steps taken for the assessment of the product

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

Rapporteur: **Kristina Dunder** Co-Rapporteur: **Martina Weise**

CHMP Peer reviewer: **Alar Irs**

- The application was received by the EMA on 24 November 2010.
- The procedure started on 15 December 2010.

- The Rapporteur's first Assessment Report was circulated to all CHMP members on 4 March 2011. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 17 March 2011.
- During the meeting on 11-14 April 2011, 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 14 April 2011.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 19 May 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 1 July 2011.
- During the CHMP meeting on 18-21 July 2011, 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 19 August 2011.
- The Rapporteurs circulated the Second Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 5 September 2011.
- The Rapporteurs circulated an Updated Second Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 13 September 2011.
- The applicant submitted the responses to the Rapporteurs' List of Outstanding Issues on 14 Sept 2011.
- During the meeting on 19-22 September 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting an extension to the Marketing Authorisation of Xarelto. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 21 September 2011.

2. Scientific discussion

2.1. Introduction

2.2. Quality aspects

2.2.1. Introduction

Rivaroxaban 15 mg and 20 mg film-coated tablets are presented as a red and brown red, respectively, round, biconvex tablets that contain rivaroxaban as the active substance. Other ingredients in the tablet core include microcrystalline cellulose , croscarmellose sodium , hypromellose, lactose monohydrate magnesium stearate and sodium laurilsulfate. The tablet coating consists of ferric oxide red, hypromellose, polyethylene glycol and titanium dioxide. The tablets are packaged in thermoformed PP or PVC/PVDC blisters.

2.2.2. Active Substance

Manufacture – Specification- Stability

The chemical name for rivaroxaban is 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide. The active substance is of the same quality with the one used in the currently approved Xarelto 10 mg tablets. The synthetic process, controls and specifications are same as the currently approved ones.

Rivaroxaban is a class II substance in the BCS classification system. It has a low aqueous solubility, which 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.

Comparability exercise for Active Substance

Not applicable

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The additional two strengths of 15mg and 20mg have been developed using the development and manufacturing experience gained with the currently approved 10 mg strength. The same excipients have been chosen for the formulation of the tablet cores. They are of pharmacopoeial quality and are commonly used in these kinds of formulations. All dose strengths have been formulated to the same tablet size and weight. The increased amount of the active substance is compensated by a corresponding smaller amount of lactose monohydrate and cellulose microcrystalline to keep the tablet weight constant.

Adventitious agents

Not applicable

Manufacture of the product

The manufacturing process is a standard process that consists of the following main steps: fluidised-bed granulation, mixing, tabletting and film-coating. All critical process parameters have been identified and are controlled by appropriate in process controls.

Although the proposed manufacturing process has not been validated at commercial scale, the batch analysis data collected from 23 clinical batches and three production scale batches for the 20 mg strength and from 10 clinical batches and 1 commercial batch for the 15 mg strength, are sufficient to indicate that the manufacturing process is robust and can reproducibly produce finished product of consistent quality complying with the approved specifications.

In addition the applicant will perform process validation studies on the first three consecutive commercial scale batches in accordance with the approved validation protocol.

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 clinical and 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

Three pilot scale batches of each strength (20 mg and 15 mg) have been stored for long-term stability studies at 25 °C/60 % RH and 30 °C/75 % RH and for accelerated stability studies at 40 °C / 75 % RH in accordance with ICH requirements. The samples were packaged in the same commercial packaging materials as those intended for commercial manufacturing (PP blister and PVC/PVDC blister).

Thirty six months of stability data have been presented for all three batches of each strength stored at 25 °C / 60 % RH and 30 °C /75 % RH. Additionally, accelerated stability data covering a period of 6 months stored at 40 °C /75 % RH have been provided

The parameters studied are appearance, degradation products (any unspecified and total), assay, dissolution and microbial purity using the same analytical methods used for release, which have been shown to be stability indicating. Additionally hardness, disintegration and water content were tested on an informative basis using the Ph. Eur test methods.

Results from thermal and high humidity stress testing have shown that the tablets are very table, while results from a photostability study demonstrate that the tablets are not sensitive to light.

In all cases the stability results presented were satisfactory, within the predefined specifications and support the proposed shelf life for the commercially packaged product under the conditions specified in the SPC.

Comparability Exercise for Finished Medicinal Drug Product

Not applicable

GMO

Not applicable

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The quality of 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 development of the 15mg and 20 mg strengths is based largely on the currently approved Xarelto 10 mg tablets.

The active substance is well characterised and documented. It is a class II substance in the BCS classification system. Like in the case of Xarelto 10 mg tablets, 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 materials are 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.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

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.

2.3. Non-clinical aspects

2.3.1. Introduction

Overall, the pharmacological programme is comprehensive, providing a good characterisation of the pharmacological properties of rivaroxaban. Four new studies (mitochondrial protein measurement, phototoxicity, repeat dose toxicity studies, carcinogenicity studies) have been submitted in this application and give additional information.

2.3.2. Primary pharmacodynamic studies

The results from previous studies show that rivaroxaban inhibits FXa, leading to secondary changes in coagulation parameters like 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.

The results of receptor binding and enzyme inhibition demonstrated that rivaroxaban is a selective FXa inhibitor, and that pharmacological effects due to interaction with unrelated receptors/enzymes are unlikely. Rivaroxaban did not cause platelet activation or aggregation in the presence of HIT antibodies. Considering the similarity of the structure of the molecule with linezolid which was discussed in the previous procedure, a noteworthy finding is that rivaroxaban did not inhibit monoamine oxidase.

2.3.3. Secondary pharmacodynamic studies

Rivaroxaban has a structural similarity to the antibiotic linezolid, sharing the central 5-S oxazolidinone structure that has been found to be essential for antibacterial activity of the latter molecule. However, data about the antibacterial activity of rivaroxaban and selected metabolites for three Gram positive strains of bacteria suggest that neither rivaroxaban, nor metabolites M1, M2 or M15 have any antibacterial activity at relevant concentrations.

Another, related issue is the possibility of mitochondrial toxicity. Linezolid inhibits bacterial growth by binding to the heavy ribosomal subunit, thereby inhibiting bacterial protein synthesis. Mitochondrial ribosomes are similar to bacterial ribosomes and linezolid is known to inhibit mitochondrial protein synthesis too. This leads to an eventual depletion of mitochondrial-derived proteins, e.g. key components in the electron transport chain, and a loss of mitochondrial function. The absence of an antibacterial effect of rivaroxaban (and metabolites) does not necessarily imply an absence of an effect on mitochondria, as other factors, e.g. permeability, are important for the end result.

This issue has been addressed in two new studies;

- Mitochondrial protein synthesis was measured in isolated rat liver mitochondria using linezolid as positive control. Up to the limit of thermodynamic solubility in aqueous solution (5 µg/mL), rivaroxaban did not cause inhibition of mitochondrial protein synthesis.

- A study on measurement of mitochondrial protein synthesis after 4-week oral (gavage) administration in rats revealed that rivaroxaban did not affect protein synthesis and activity of mitochondrially encoded respiratory chain complex proteins and thus, rivaroxaban did not show any linezolidlike mitochondrial toxicity.

2.3.4. Safety pharmacology programme

The safety pharmacology studies do not suggest that any acute adverse exaggerated pharmacological effects of rivaroxaban, except bleeding, are likely. Pharmacokinetic data, showing that the animals were adequately exposed, were collected in several studies. However, it should be noted that the safety pharmacology results were obtained after a single dose of rivaroxaban. Consequently, the safety pharmacology programme was not designed to detect any long-term pharmacological effects like adaptation and rebound phenomenons. Some of the findings in the repeated dose toxicology studies may, at least partly, depend on the primary pharmacological mechanisms of rivaroxaban.

2.3.5. Pharmacodynamic drug interactions

There are no pharmacodynamic drug interactions submitted in this application.

2.3.6. Pharmacokinetics

Non-clinical ADME studies were conducted mainly in rats (Wistar) and dogs (Beagle). Toxicokinetic data were collected from repeated dose studies in mice (CD-1) rats, dogs and female rabbits (CHBB). General organ distribution was studied in Wistar rats and pigmented rats (Long Evans); placental transfer and excretion into milk was studied in female Wistar rats.

In addition, plasma protein binding and metabolism data was generated in vitro for several species, including Cynomolgus monkeys and humans. Several in vitro studies were made to characterise the involvement, inhibition and induction of 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 a maximal plasma concentration in about 0.5 hours after oral administration in both rats and dogs. 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. There was also a gender difference in rats, with higher exposure in the females.

Protein binding varied between species, being highest in the rat (98.7%) and lowest in the 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 is unremarkable, showing the highest concentrations in the gastro-intestinal tract, liver and kidneys, and low concentrations in the brain. The distribution in pigmented rats was similar but could not exclude some affinity to melanin. Rivaroxaban passes the placenta barrier but does not accumulate in the foetuses. The substance is excreted into rat milk.

Rivaroxaban is subject to oxidative metabolism in the liver. The main metabolic pathway is catalysed by CYP2J2 and CYP3A4. The metabolism is qualitatively similar in man and the toxicology species and there were no unique human metabolite. The rat differs from dogs and humans with a higher proportion of rivaroxaban + metabolites excreted in bile/faeces, and a lower proportion excreted in the urine.

Both P-gp and BCRP are most likely involved in the renal excretion of rivaroxaban.

In conclusion, the pharmacokinetic profile of rivaroxaban is well known. Additional studies provided new data regarding human BCRP substrate characteristics. The studies showed that rivaroxaban

caused only a slight inhibition of Bcrp in in vitro studies. This is considered not to be of clinical relevance.

Ketoconazole and ritonavir caused an increase of rivaroxaban plasma exposure and a decrease of renal clearance of rivaroxaban in clinical drug-drug interaction studies. This finding is most likely the result of the combined oxidative CYP3A4/3A5-catalyzed oxidative metabolic pathway and the inhibition of the transporter-mediated active renal secretion of rivaroxaban. Both drugs (ketokonazole and ritonavir) exhibited only a moderate exposure increase of rivaroxaban in vivo. As a conclusion, the pharmacokinetic profile of rivaroxaban was not altered by the additional studies.

2.3.7. Toxicology

2.3.7.1. Repeat dose toxicity

With this application, oral repeat dose toxicity studies have been performed in the mouse (4-13w), the rat (4-13-26w) and in the dog (4-13-52w) to support long term use in patients.

The clinical crystal formulation of rivaroxaban (micronized) was used in two of the repeat-dose studies and in the carcinogenicity studies. The oral toxicity profile in each species could be investigated up to relatively high systemic exposures of unbound fraction of rivaroxaban without that no apparent MTD was reached in the rodent species. In the dog, MTD was reached at high dose in the 13- and 52-week studies (23x and 14x clinical exposures in terms of $AUC_{unbound}$, respectively).

Main findings in mice, seen from the low dose level tested (margin of unbound AUC exposure of 3x and 4x for M and F, respectively) were significant decrease in leucocyte count and effects on the liver. Decreased leucocyte count was evident in all four studies. With the clinical crystal formulation of rivaroxaban (micronized), focal liver necrosis together with increased liver weight (abs+rel) and decreases in liver proteins were determined (serum ASAT and ALAT, activities of ECOD/EROD/ALD/GLU-T) from LD. In the two other 13 weeks studies, using other formulations, sporadic focal liver necrosis were seen also, but overall, no clear relationship to exposure was identified. In the newly submitted carcinogenicity study in mice there was a numerical increased incidence of tumors with dose but with no increase in foci of hepatocellular alteration.. Hepatic tumors were also within expected control ranges (see further below). These findings suggest that rivaroxaban induced some effects on the liver in mice, but as further described below, there were no obvious signs of hepatic toxicity in either the rat or dog. Furthermore, the long-term clinical studies do not reveal signs of hepatotoxicity.

In rat, no treatment-related mortality was reported in the oral studies. In the study using the clinical crystal formulation of rivaroxaban (PH-34379, 13-week study), different treatment-related effects were determined from the lowest dose levels tested (no NOAEL, margin of unbound AUC exposure of 2.0x and 4.1x for M and F, respectively): increase in urine output, liver (periportal inflammatory infiltrates/megacaryocytes, transient increase in ALAT and unspecific biomarker of cell leakage LDH, decrease in glutamate dehydrogenase, GLDH, with highest activity in periacinar hepatocytes), decrease in heart weight (abs+rel), pancreatic acinar hypertrophy, optic nerve fiber degeneration, and poplietal lymph node pigmentation. From next dose level, sporadic liver lesions were noted in single animals. In the other oral studies using the nonclinical crystal co precipitate formulation of rivaroxaban (PEG 6000 melt coprecipitate, treatment-related effects were increased amount of IgG and IgA (from LD at 4 and 13w of treatment; not measured in the 26w study) and increased incidence of pancreatic lesions (from LD in the feeding study). At higher dosing, urine crystals formation together with increased creatinine

and urea content and increased incidence of ovary follicle cysts were noted in the 26w study from MD. Slight to marked increase in sperm granuloma was determined in HD animals of 4 and 26w studies.

The studies with the PEG 6000 melt coprecipitate formulation revealed that ALAT increased transiently up 1-3 month of treatment without any signs of liver lesions at autopsy 2-3 months later (from LD in the 26w study). There were also signs of decrease in absolute and relative heart weight. Myocardiopathy was noted in two HD female rats of the 26 week study, but those occurred at very high exposure levels. Although there was a relatively small but consistent decrease in heart weight in most rat studies, there was overall no histological correlate in the heart. Thus, the toxicological as well as clinical relevance of the finding of decreased heart weight is uncertain / unknown.

In dog, coagulation time data (PT and/or PTT) suggested treatment resistance development. Consequently, bleeding related observations was greater at w13 than at w52. No study was conducted with the clinical crystal formulation of rivaroxaban, instead the PEG 6000 melt coprecipitate formulation was used. Slight dose-dependent increase in liver weight was seen in the 4 w study (with minimal periportal vacuolation and centrilobular fat) but not in the longer studies. Four male dogs of the 52 w study (2LD/2MD) had minimal/slight cytoplasmic vacuoles/inclusions in the liver.

In the kidney, treatment-related increase in the incidence of small dense nuclei of collecting duct epithelial cells was reported from LD in males of the 52w study (no NOAEL).

No effect on ECG, BP, reflex, ophthalmology, urinalyses, hormone (T3, T4), and liver N-demethylase, O-demethylase, P450 and TG, was reported. Overall, there was no indication of hepatic or cardiac toxicity identified in the dog. Furthermore, there was no finding of optic (nerve) toxicity in dogs. Thus, the slightly higher incidence of optic nerve degeneration seen in some rat studies is not considered a cause of concern, since the pigmented dog eye is considered more relevant for assessing effects on eye, than the albino rat.

2.3.7.2. Genotoxicity

Rivaroxaban was tested negative in the standard battery for genotoxicity testing as part of the initial Marketing Authorisation.

2.3.7.3. Carcinogenicity

The carcinogenic potential of rivaroxaban was tested in 2-year studies in mice and rats. Dose selection was based on a limit of absorption of microcrystalline rivarixaban at 60 mg/kg.

Both studies were performed as gavage studies applying doses of 10, 20 and 60 mg/kg of micronized rivaroxaban. Study details and major observations in neoplastic lesions are summarized in table below.

Table: Carcinogenicity studies performed with rivaroxaban

Type of test/Study ID/ReportID/GLP	**Test substance batch**	**Dose [mg/kg/d] / Route / animals/group**	**Mean (n=20) plasma conc. [Cmax ng/ml, AUC ng*h/m] at steady state**	**Major findings**
Mouse				
Carcinogenicity in CD-1 mice **T 3076596 / PH-36243 / yes**	BX023BS, BXA18UX	0, 10, 20, 60 / p.o gavage. / 60/sex/group, + 20/sex/group for toxicokinetics	week 52 Cmax 10 mg: f 568, m 363 20 mg: f 963, m 503 60 mg: f 1020, m 1090 AUC 10 mg: f 1590, m 871 20 mg: f 2370, m 1240 60 mg: f 3090, m 2520	increase in hepatocellular adenoma and carcinoma in males (Exact Peto trend test p=0.0089) slight increase in malignant lymphoma in high dose male and mid and high dose female (not significant with Exact Peto trend test)

Type of test/Study ID/ReportID/GLP	Test substance batch	Dose [mg/kg/d] / Route / animals/group	Mean (n=20) plasma conc. [Cmax ng/ml, AUC ng*h/m] at steady state	Major findings
Rat				
Carcinogenicity in Wistar rats **T8076429 / PH-36242 / yes**	BX023BS, BXA18UX	0, 10, 20, 60 / p.o gavage. / 50/sex/group, + 20/sex/group for toxicokinetics	week 56 Cmax 10 mg: f 4610, m 1890 20 mg: f 5480, m 2310 60 mg: f 7810, m 2310 AUC 10 mg: f 34700, m 13400 20 mg: f 47500, m 15400 60 mg: f 48200, m 20300	non statistically significant increase in neoplastic lesions, in female rats slight increases in mammary gland fibroadenomas in high dose, adrenal gland adenomas in mid and high dose, and clitoral gland squamous cell carcinoma in high dose

The selected doses were 10, 20 and 60 mg/kg. At these doses the margins of exposure when compared to the human plasma levels at 20 mg/day were only 0.4, 0.6, 1.0 and 0.7, 1.3, 1.6 in males and females, respectively, and in the rat study 1.0, 1.2, 1.5 and 2.6, 3.6, 3.6 in males and females, respectively. Administration of rivaroxaban as PEG 6000 melt coprecipitate formulation had resulted in higher systemic exposure. However, the melt coprecipitation process led to the formation of a genotoxic anilino-morpholinone which was considered to imply a risk of false positive results in carcinogenicity testing. The dose selection was agreed with the EMA in a scientific advice. The dose selection is acceptable considering the limit of absorption of microcrystalline rivarixaban and risk of false positive results with the PEG 6000 melt coprecipitate formulation.

In mice, necropsy revealed a numerical increase in the incidence of macroscopic liver lesions that corresponded to an apparently higher incidence of hepatocellular tumors in males. The increase was however not statistically significant in the trend test and the pair-wise comparisons. Further, no consistent pattern of foci was seen. The observed incidence of hepatocellular tumors as well as slightly higher incidence of malignant lymphomas is within the high spontaneous variability of these tumors in male CD-1 mice.

The slightly higher incidence of ovarian hemorrhage at 10 mg/kg and above and at 60 mg/kg a higher number of animals showing pigment deposition as well as the higher incidences of extramedullary hematopoiesis in the spleen seen in males may be secondary to the pharmacological mode of action of rivaroxaban. Taken together, the data do not support a carcinogenic effect of rivaroxaban.

In the rat carcinogenicity study, there was an increased number of valvular fibrosis in the heart, both in treated males (0/50 [control], 1/50 [low dose], 1/50 [mid dose] and 2/49 [high dose]) and females (0/50 [control], 0/50 [LD], 2/50 [MD] and 4 /50 [HD]). The report states that since the incidence was only marginally higher compared to control and statistical significance was missing no toxicologically relevance is considered. Although the incidence is relatively low, there is a dose –related increase; and there is no case in the control group of either sex. Thus, a relation to treatment cannot be excluded. Given that this finding is considered a safety concern, the Applicant was asked to further address this issue and submitted a review of all repeat dose toxicity data and mechanistic data regarding serotonin interaction was submitted which provided no support that rivaroxaban induced valvular fibrosis.

All in all, the different aspects addressed in the MAH´s response lead to the conclusion that the observed numerically increased incidence of valvular fibrosis in rats most likely is a finding reflecting the variability of age-related cardiac alterations rather than related to the treatment with rivaroxaban.

The MAH has made search of valvular heart disease and of heart failure in the clinical trial database and in spontaneous postmarketing reporting. There are no indications of drug induced valvulopathy in the clinical data collected so far.

Thus, there is no need to include 'valvulopathy' as a potential or identified risk in the RMP.

In high dose female rats, in the pituitary gland a reduced number of nodules and in the ovaries a reduced number of cysts were seen. In the preputial glands of male rats treated at 60 mg/kg, a higher number of nodules were observed, but with no evidence of an increased rate of neoplasms. A slight not statistically significant numerical increase in adrenal cortical adenomas was observed in females at 20 and 60 mg/kg. Fibroadenomas in the mammary gland and squamous cell carcinoma in the clitoral gland were more often seen in females at 60 mg/kg, but did not reach the significance levels for common tumors. An increased pigment deposition was seen in several organs at 60 mg/kg most likely represent residues of mode of action-related bleedings. None of these findings suggest a carcinogenic potential for rivaroxaban.

In conclusion, rivaroxaban did not show a carcinogenic potential when tested in mice and rats up to 60 mg/kg.

2.3.7.4. Reproduction Toxicity

In the initial Marketing authorisation application, reproductive toxicity studies have been performed in rat and rabbit and the results suggest a teratogenic effect at clinically relevant exposure. All effects have been proposed to be related to rivaroxaban's pharmacodynamic activity and pregnancy and breastfeeding have been contraindicated. The latter is endorsed while an additional true placenta and teratogenic effects of rivaroxaban cannot be excluded.

2.3.7.5. Other toxicity studies

Phototoxicity

Rivaroxaban was tested negative in a phototoxicity test in mammalian cell.

2.3.8. Ecotoxicity/environmental risk assessment

Summary of main study results

Substance (INN/Invented Name): Rivaroxaban			
CAS-number (if available): 366789-02-8			
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	0.15	µg/L	> 0.01 threshold (Y)
Phase II Physical-chemical properties and fate			
Study type	**Test protocol**	**Results**	**Remarks**
Adsorption-Desorption	OECD 121	K_{oc} =316	accepted only for Tier A
Ready Biodegradability Test	OECD 301	not readily biodegradable	OECD 308 is required.
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50, water}$ = $DT_{50, sediment}$ = $DT_{50, whole\ system}$ = 51.9 d (worst case) % shifting to sediment =35,4	Not required if readily biodegradable
Phase IIa Effect studies			

Study type	Test protocol	Endpoint	value	Unit	Remarks
Daphnia sp. Reproduction Test/*Daphnia magna*	OECD 211	NOEC	500	µg/L	No risk.
Fish, Early Life Stage Toxicity Test/*Danio rerio*	OECD 210	NOEC	86	µg/L	No risk.
Phase IIb Studies					
Sediment dwelling organism/ *Chironomus sp.*	OECD 218	NOEC	100	mg/ kg	No risk.

Since in Phase I the action limit of the predicted environmental concentration in surface water ($PEC_{surface\ water}$) is exceeded the applicant submitted a Phase II environmental risk assessment (ERA) for the active ingredient rivaroxaban.

As the action limit for the $PEC_{surface\ water}$ of 0.01µg/l is exceeded the applicant provided a detailed Phase II environmental risk assessment for the active ingredient rivaroxaban. On the basis of the provided dataset the applicant concluded that no risk for the environment can be expected from the introduction of rivaroxaban from Xarelto.

To complete the environmental risk assessment the applicant was asked more information in particular in relation to the log P_{ow} determination, the water-sediment study and the studies according OECD 201 and 209. On the basis of the correct octanol/water partition coefficient of log P_{OW} = 1.5, no study on bioaccumulation in fish (OECD 305) is required according to the ERA guideline CHMP/SWP/4447/00 (June 2006), because the trigger value for this study of log P_{OW} = 3 is not reached.

In conclusion, all remaining issues have been addressed and the Applicant´s responses were considered acceptable. As a result, the data allow to conclude that ribaroxaban does not have a potential risk to the environment.

2.3.9. Discussion on non-clinical aspects

Overall, the non-clinical programme is comprehensive providing a good characterisation of the properties of rivaroxaban. The majority of non-clinical studies were assessed in connection to the previous approval of the 10 mg tablet and together with the new studies the documentation overall support chronic treatment with the higher dose in the sought indication. Concerns were expressed regarding the finding of valvular fibrosis in the heart of rivaroxaban treated animals in the rat carcinogenicity study. However, the observed numerically increased incidence of valvular fibrosis in rats is considered most likely a finding reflecting the variability of age-related cardiac alterations rather than related to the treatment with rivaroxaban.

2.3.10. Conclusion on the non-clinical aspects

The additional non clinical studies submitted to support the additional strengths of 15 and 20 for a new indication provide additional information on the use of rivaroxaban in animal studies. Overall the data support the use in humans for the proposed indication for VTE and DVT treatment.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

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.

2.4.2. Pharmacokinetics

The applicant has submitted additional clinical pharmacology studies characterising the dose proportionality of the 15 and 20 mg new strengths compared to the approved 10 mg tablet and characterising the food effect on the 20 mg strength. The application also included a population PK and PK/PD evaluation of phase II studies in patients treated for DVT.

Table 1 displays additional clinical pharmacology studies submitted with this application. Pharmacokinetic data were also obtained in patients from two phase II studies. Plasma rivaroxaban concentrations were measured using a validated HPLC-MS/MS method. Pharmacokinetic parameters in phase I studies were calculated by non-compartmental methods. Nonlinear mixed effects modelling (population pharmacokinetic analysis) was used to evaluate pharmacokinetics in patients.

Table 1 Clinical Pharmacology studies

Study no.	Report No.	Type of study	Dose [mg]	Subjects exposed to Rivaroxaban (n)	Subjects exposed to placebo (n)
Special Populations (effect of intrinsic factors)					
12980	R-8560	PK, PD in CHF patients	10	18	8
Interaction Studies (effect of extrinsic factors)					
10849	PH36332	Warfarin interaction, multiple dose	20	56	0
Specific Purpose Studies					
11940	PH-36253	Perfusion chamber, single dose with and without Aspirin®	5, 10, 20	39	0
Biopharmaceutical Studies[b]					
11938	PH-35231	Food effect with final formulation, single dose	20	23	0
12362	PH-36272	Dose-proportionality with food	10, 15, 20	24	0
13371	A45677	Bioequivalence	15	20	0
14022	PH-36262	Relative bioavailability of an oral suspension for pediatric use	10, 20 (oral suspension) 10 (tablet)	17	0
14588	PH-36254	Bioequivalence	2x5, 10	28	0

The absolute bioavailability of the 20 mg strength in fasting state was previously determined to be 66%. A high-calorie, high-fat breakfast increased rivaroxaban AUC by 39% and C_{max} by 76%. Absorption was delayed in the fed state showing a lag-time of approximately 1.5 h and a delay in median t_{max} of about 1.25 h. The food effect on the 15 mg strength was not evaluated in a specific study. However a cross-study comparison suggests an 18% increase in AUC and 86% increase in Cmax with food.

The assessment of the initial marketing authorisation application concluded that rivaroxaban displays dose dependent pharmacokinetics with less than proportional increase in AUC as the dose is increased.

The non-linearity is most marked in fasting state, where the non-linearity starts at doses above 15 mg. However, in fed state the pharmacokinetics seemed to be fairly proportional up to 30 mg in Caucasian volunteers and to 20 mg in Japanese and Chinese volunteers. A ceiling effect with no additional increase in exposure with increased dose is reached at doses of about 50 mg.

The additional Study 12362 demonstrated dose proportional increase in AUC and Cmax with increased dose in the dose range 10 to 20 mg in fed state. There is a trend for less than proportional increase in Cmax with dose and slightly longer $t_{1/2}$ at the 20 mg dose, reflecting a slightly slower absorption with increased dose and the absorption rate limited elimination. The population pharmacokinetic analysis included dose as a covariate with a relative bioavailability of 79% at the 20 mg dose compared to the 10 mg dose, hence suggesting a small deviation from dose proportionality in patients.

The population PK and PK/PD analysis included 870 patients from the phase II ODIXa-DVT and EINSTEIN-DVT studies. The PK of rivaroxaban was described by an oral, one-compartment model, with clearance (CL/F), volume of distribution (V/F) and a first-order absorption rate (ka) as parameters. Rivaroxaban clearance was estimated to be 5.67 L/h, with inter-individual variability of 39.9%. Volume of distribution was estimated to be 54.4 L, with inter-individual variability of 28.8%, similar to that observed with healthy subjects. Age and serum creatinine were identified patient covariates potentially affecting rivaroxaban clearance and body weight and sex as covariates on volume of distribution.

The covariates identified are expected from previous studies in special populations and the covariate effects observed are of a similar magnitude as previous population PK analysis in surgery patients and of a somewhat smaller magnitude than specific studies in special populations. Hence, there are no unexpected results from this analysis.

Special populations

As the current application concerns use of rivaroxaban in a new population at a higher dose, the treatment recommendations in special populations was reviewed in particular in eldery, in patients with moderate or severe renal impairment or moderate hepatic impairment and in patients with a combination of risk factors that increase rivaroxaban exposure.

The applicant proposes a contraindication in patient with coagulopathy including cirrhotic patients with Child Pugh B. It is agreed that cirrhotic patients with Child Pugh B (moderate hepatic impairment) have increased risk for bleeding and should be contraindicated. The increased exposure in the elderly is to a large extent caused by reduced renal function. Consequently dose reduction based on age alone is not considered needed. The SPAF population consists mostly of elderly patients and there is extensive experience in treating elderly patients with rivaroxaban 20 mg q.d. In patients with moderate or severe renal impairment (creatinine clearance 15-49 ml/min), the applicant recommends a reduction of the maintenance dose from 20 mg once daily to 15 mg once daily

Based on PK modelling, the exposure in patients with moderate or severe renal impairment treated with 15 mg q.d. and with co-administration of moderate CYP3A4 inhibitors is in a similar range as patients with mild renal impairment and no CYP3A4 inhibitors where extensive safety information is available. Hence, it is agreed that caution is not needed in these patients. However, additional increase in exposure is expected in patients with potent CYP3A4 inhibitors. Caution is therefore advised in patients with renal impairment co-administered potent CYP3A4 inhibitors (e.g. chlarithromycin, telithromycin).

2.4.3. Pharmacodynamics

Mechanism of action

Rivaroxaban is a competitive, selective and direct oral factor Xa inhibitor. Activation of factor X to factor Xa plays a central role in the cascade of blood coagulation. Inhibition of factor Xa would be expected to inhibit the amplified burst of thrombin generation induced when the coagulation system is activated both when the activation is initiated by the internal ("surface activation") or external rout (tissue factor and factor VIIa).

Primary and Secondary pharmacology

In phase I dose escalation studies, factor Xa was inhibited in a dose-dependent way over the complete dose range closely following the pharmacokinetic profiles of rivaroxaban. The other global clotting tests PT, aPTT, and Heptest were also affected in a dose-dependent way. The 10 mg dose of rivaroxaban resulted in a maximal reduction of the factor Xa activity by 33% (SD 5.1%), and a maximal prolongation of PT of 38%. The 20 mg dose of rivaroxaban resulted in a maximal reduction of the factor Xa activity by 55%, and a maximal prolongation of PT of 98%. All pharmacodynamic parameters investigated in phase I trials correlated closely with the plasma concentrations. Rivaroxaban has no influence on antithrombin III levels or factor II, thus supporting the direct mechanism of inhibition of factor Xa in humans.

Results of investigations of the ETP (endogenous thrombin potential) have shown that single doses of 5 and 30 mg rivaroxaban influence the intrinsic and extrinsic pathway of the coagulation system. A dose-dependent influence is noted on lag-time, time to peak, peak level and total amount of the endogenous thrombin over time curve.

Another study identified a prolonged influence of rivaroxaban beyond 24 h on the peak level of the ETP as well as lag time suggesting that pharmacological effects may be present beyond 24 hours after doses of 20 mg.

With regard to secondary pharmacology effects it can be noted that neither preclinical data nor the dedicated QT study indicate that rivaroxaban affects QT to any clinically relevant extent.

From a clinical point of view the primary pharmacology of rivaroxaban has been well characterised.

Exposure response

The relationship between plasma concentration and effect was evaluated in the population PK/PD analysis of data from the two phase 2b dose-ranging studies. A linear intercept model for PT, an Emax model for Factor Xa activity, and a combined linear-Emax model for the HepTest were used. Observed rivaroxaban concentrations were used as input in the PK/PD models. Rivaroxaban plasma concentrations up to 700 μg/L correlated with PT in an almost linear fashion. The slope of the correlation became non-linear at higher rivaroxaban plasma concentrations. At steady state, baseline PT was estimated to be 12.5 seconds and the slope of the correlation was 3.3 seconds/100 μg/L. For FXa the baseline FXa activity value differed somewhat between studies and study days and ranged between 0.9 and 1.1 U/mL and the EC50 of rivaroxaban was 376 μg/L and Emax 98.4%. The PK/PD parameter estimates for PT were very similar in the above analyses and those previously obtained when using Neoplastin in surgery patients. The EC_{50} for FXa was somewhat higher than that estimated in surgery patients (376 compared to 296 ug/l).

A post-hoc, exploratory analysis of the relationship between estimated steady-state $AUC_{0\text{-}24h}$, C_{max} and C_{trough} and adjudicated efficacy and bleeding events was evaluated in rivaroxaban treated subjects from Studies 11223 and 11528 (PH-34764). The analysis included also evaluation of dose and exposure categorised in low, middle and high exposure groups. The analysis suggested that the

decrease in incidence of a VTE deterioration until week 12 was best correlated to C_{trough} values, while any/clinically relevant bleeding events tend to show the most pronounced increase with higher values of $C_{max.}$ To some extent this evaluation supports the selected dose. The obtained exposure response relationships suggest that the gain in efficacy with a higher dose than the proposed would be marginal while there is an increased bleeding risk at higher exposure.

Pharmacodynamics when switching from warfarin to rivaroxaban

A placebo controlled study in healthy males has been performed to investigate the pharmacodynamics when switching from warfarin to rivaroxaban. The study was carried out in a 3 group parallel design: In treatment group A warfarin was titrated to an INR of 2 to 3, and rivaroxaban was started 24 hours after stopping of warfarin. In treatment B warfarin was titrated to an INR of 2 to 3 and placebo was started 24 hours after stopping of warfarin. In treatment C rivaroxaban was given without any warfarin pretreatment. Rivaroxaban was administered once daily as a 20 mg dose over 4 days (Day 0d to 3d). In the warfarin treated groups, warfarin preceded rivaroxaban and placebo and was given in doses of 2.5 to 15 mg once daily aiming to increase INR to values between 2.0 and 3.0 for each subject. 84 subjects were included in the PK/PD set, 28 subjects per treatment group.

After switching from steady state warfarin to 20 mg rivaroxaban at INR values between 2.0 and 3.0, over-additive agonistic effects were observed for PT (s) and PT (INR). PT prolongation was 4.4 times baseline (45 seconds) after the switch compared to 1.6 times baseline (7 seconds) after rivaroxaban alone.

INR values above 3.0 were observed in all 28 subjects on Day 0d and remained above this value for a mean of 12.6 hours. After dosing on the following Day 1d, 25 subjects showed INR values above 3.0 which remained there for a mean of 7.5 hours and 8 subjects on Day 2d. After Day 2d, no subject with PT INR values greater than 3 was observed.

Rivaroxaban enhanced the effect of warfarin on Factor Xa activity, aPTT, and ETP. Combined effects were additive for Factor Xa activity and roughly additive for ETP and aPTT. Rivaroxaban induced changes were reversible within 24 hours.

The Applicant has provided an update on the development of PK/PD markers to be recommended in clinical use. A prothrombin time assay and a factor Xa inhibition test are the most promising tests that after further investigations possibly could be recommended for use in clinical routine. The concentrations of rivaroxaban as measured in the clinical trials during treatment for DVT are given in the updated SPC.

Anti-Factor Xa, HepTest and PiCT were not affected by warfarin. Tests of anti-Factor Xa, HepTest and PiCT were capable of detecting rivaroxaban effects independently from warfarin effects.

2.4.4. Discussion on clinical pharmacology

The applicant has provided additional studies evaluating the dose proportionality of the additional strengths and the food effect on the 20 mg strength. A population PK analysis provides pharmacokinetic data in the target population. These additional data are considered adequate to support the use in the new indication.

2.4.5. Conclusions on clinical pharmacology

The pharmacokinetic documentation is considered sufficient and supports the approval of the two new strengths in the proposed indication.

2.5. Clinical efficacy

2.5.1. Dose response studies

Two dose response studies were performed in patients with acute DVT.

Table E-1 Dose response studies in treatment of VTE

Study number/ primary indication	Design	Rivaroxaban regimen and treatment duration	Comparator and treatment duration	Number of subjects randomized to rivaroxaban	Numberof subjects randomized to enoxaparin/VKA treatment
Supportive phase II trials					
11223 acute symptomatic DVT without symptomatic PE	randomized, partially blinded (double-blind for rivaroxaban and open-label for the comparator),parallel-group	10 mg b.i.d., 20 mg b.i.d., 30 mg b.i.d. and 40 mg o.d. 12 weeks	Enoxaparin b.i.d. overlapping with and followed by VKA 12 weeks	487 R 478 VFS 431 ITT 419 PP	126 R 126 VFS 112 ITT 109 PP
11528 acute symptomatic DVTwithout symptomatic PE	randomized, partially blinded (double-blind for rivaroxaban and open-label for comparator),parallel-group	20 mg, 30 mg and 40 mg o.d. 12 weeks	(LMW) heparin overlapping with and followed by VKA 12 weeks	406 R 405 VFS 368 ITT 348 PP	137 R 137 VFS 126 ITT 101 PP

Study 11223 was a proof-of-principle and dose-ranging study in subjects with confirmed acute proximal DVT.

Study 11528 was a dose-ranging study in subjects with proximal or extensive calf-vein thrombosis (i.e. involving at least the upper third part of the calf veins).

For both studies, the assessment of all efficacy and safety outcomes was done by central and independent adjudication committees, which were unaware of treatment allocation.

In study 11223, the primary efficacy outcome was the response to treatment based on repeat CUS at 3 weeks. A 'positive response' was defined as an improvement by at least 4 points in the CUS score compared to baseline. Any confirmed symptomatic VTE (i.e. recurrent DVT, non-fatal PE or fatal PE, including unexplained death for which PE could not be ruled out) up to Day 21 was defined as 'negative response'

There were three TE events in the ITT population – 1 proximal DVT in the 10 mg b.i.d. treatment group and 1 in the 20 mg b.i.d. treatment group as well as 1 non-fatal PE in the 30 mg b.i.d. treatment group).

Table E-2 Response to treatment based on CUS thrombus score and confirmed VTE events at visit Day 21 (Study 11223)

Cut Off Score		Rivaroxaban 10 mg b.i.d.	Rivaroxaban 20 mg b.i.d.	Rivaroxaban 40 mg o.d.	Rivaroxaban 30 mg b.i.d.	VKA / enoxaparin
ITT population		(N=106)	(N=100)	(N=114)	(N=111)	(N=112)
4 points [b]						
	Unchanged	48 (45.3%)	40 (40.0%)	65 (57.0%)	47 (42.3%)	60 (53.6%)
	Improved	57 (53.8%)	59 (59.0%)	49 (43.0%)	63 (56.8%)	52 (46.4%)
	Deteriorated	1 (0.9%)	1 (1.0%)	0 (0.0%)	1 (0.9%)	0 (0.0%)
30% change						
	Unchanged	48 (45.3%)	51 (51.0%)	69 (60.5%)	52 (46.8%)	67 (59.8%)
	Improved	56 (52.8%)	48 (48.0%)	43 (37.7%)	58 (52.3%)	45 (40.2%)
	Deteriorated	2 (1.9%)	1 (1.0%)	2 (1.8%)	1 (0.9%)	0 (0.0%)

Table E-3 Incidence rates of all bleeding events (safety population) (Study 11223)

Bleeding event	BAY 59-7939 10 mg bid (N=119) n (%)	BAY 59-7939 20 mg bid (N=117) n (%)	BAY 59-7939 40 mg od (N=121) n (%)	BAY 59-7939 30 mg bid (N=121) n (%)	VKA / enoxaparin (N=126) n (%)
Any event	6 (5.0%)	11 (9.4%)	14 (11.6%)	13 (10.7%)	8 (6.3%)
Major bleeding	2 (1.7%)	2 (1.7%)	2 (1.7%)	4 (3.3%)	0 (0.0%)
Fatal bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Clin overt bleeding[b]	2 (1.7%)	2 (1.7%)	2 (1.7%)	2 (1.7%)	0 (0.0%)
Clin overt bleeding[c]	2 (1.7%)	0 (0.0%)	1 (0.8%)	2 (1.7%)	0 (0.0%)
Clin overt bleeding[d]	1 (0.8%)	2 (1.7%)	1 (0.8%)	3 (2.5%)	0 (0.0%)
Non-major bleeding	4 (3.4%)	9 (7.7%)	12 (9.9%)	11 (9.1%)	8 (6.3%)

a Bleeding events starting more than 2 days after last study medication intake were not considered.
b Associated with a fall in Hb of ≥2 g/dL.
c Leading to transfusion of ≥2 units blood.
d Warranting treatment cessation.

In study 11528, the primary efficacy outcome was the composite of symptomatic recurrent DVT or symptomatic non-fatal or fatal PE (including unexplained death for which PE could not be ruled out) or deterioration in thrombotic burden, as assessed by repeat CUS and perfusion lung scan (PLS) at Week 12.

Table E-4 Overall response to treatment based on CUS, PLS, and confirmed symptomatic VTE on Day 84 (Study 11528)

Overall response	Rivaroxaban 20 mg o.d.	Rivaroxaban 30 mg o.d.	Rivaroxaban 40 mg o.d.	(LMW) heparin/ VKA
ITT population	(N=123)	(N=119)	(N=126)	(N=119)

Overall response	Rivaroxaban 20 mg o.d.	Rivaroxaban 30 mg o.d.	Rivaroxaban 40 mg o.d.	(LMW) heparin/ VKA
Improved	95 (77%)	98 (82%)	93 (74%)	82 (69%)
Unchanged	19 (15%)	14 (12%)	25 (20%)	26 (22%)
Deteriorated	9 (7%)	7 (6%)	8 (6%)	11 (9%)

The number of events for recurrent DVT or PE or death of any cause up to day 98 was 3, 5, 2 and 8 in the 20 mg o.d., 30 mg o.d., 40 mg o.d. and the LMWH/VKA groups respectively.

Table E5 Incidence rates of clinically relevant bleeding events (major or clinically relevant non-major bleedings)

Bleeding event	BAY 59-7939 20 mg od (N=135)	BAY 59-7939 30 mg od (N=134)	BAY 59-7939 40 mg od (N=136)	(LMW) heparin/ VKA (N=137)
Any event	31 (23.0%)	29 (21.6%)	29 (21.3%)	38 (27.7%)
Major bleeding	1 (0.7%)	2 (1.5%)	0 (0.0%)	2 (1.5%)
Fatal bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
Critical bleeding	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (1.5%)
Intracranial	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
Rectal	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
Clinically overt bleeding associated with a fall in hemoglobin ≥2 mg/dL	1 (0.7%)	1 (0.7%)	0 (0.0%)	1 (0.7%)
Clinically overt bleeding leading to blood transfusion ≥2 units of blood	1 (0.7%)	2 (1.5%)	0 (0.0%)	1 (0.7%)
Non-major bleeding	30 (22.2%)	27 (20.1%)	29 (21.3%)	36 (26.3%)
Any clinically relevant non-major bleeding	7 (5.2%)	6 (4.5%)	3 (2.2%)	10 (7.3%)

Final dose regimen chosen

Thrombus scores were evaluated with compression ultrasonography (CUS) in study 11223 and with CUS and perfusion lung scint (PLS) in study 11528.

In the phase II dose-finding studies, there was no dose response relationship or clear efficacy advantage observed for b.i.d. dosing compared with o.d. dosing over the range of rivaroxaban doses tested, and no definitive difference between the b.i.d. and o.d. regimens was seen in bleeding compared to LMWH-VKA, except at 40 mg TDD or higher. The o.d. dosing was considered advantageous from a patient convenience and compliance perspective. However, b.i.d. dosing had some advantages; steady state was attained earlier, higher trough levels were reached, an improved duration of anticoagulation was noted, and a better (but non-significant) improvement in thrombus score was obtained with twice daily dosing. It was therefore determined that including b.i.d. dosing initially in the rivaroxaban regimen for the phase III program could provide the intensification needed and permit continuous rivaroxaban therapy without first requiring the use of a heparin in the initial acute DVT treatment phase. Also, based on the clinical observations from the phase II dose-finding trials, it was concluded that the lowest once-daily dose studied (20 mg) should be selected as the dose beyond the initial intensification stage for phase III VTE treatment trials. Analysis of the 2 dose-finding studies in subjects with acute symptomatic DVT in conjunction with prior knowledge and experience in the field of VTE treatment indicated that rivaroxaban 15 mg twice-daily for an initial 3-week period, followed by once-daily administration of 20 mg for the subsequent treatment period, would be the optimal regimen to study in the phase III program.

In study 11223, a 30% improvement in CUS thrombus score was observed in 53, 48, 38, 52 and 40% in the 10mg b.i.d, 20mg b.i.d, 40mg o.d., 30mg b.i.d and enoxaparin/VKA groups, respectively. In study 11528 the overall improvement rates based on CUS, PLS and symptomatic DVT were 77, 82, 74 and 69% in the 20mg o.d., 30mg o.d., 40 mg o.d. and the enoxaparin/VKA groups, respectively. The lack of a clear relationship between dose and efficacy response are commonly seen in dose finding studies within this area.

There was a slight tendency for increased bleeding risks with increasing doses in study 11223 with numerically somewhat more bleedings with doses equal to or above 40 mg (with an incidence of 2 % of major bleedings and an additional 10% of non major bleedings) in comparison with enoxaparin/VKA (major bleedings 0%, non major 6%). With the dose 10 mg b.i.d. the bleeding rates were similar to those in the enoxaparin/VKA group. In study 11528 bleeding rates were similar in all treatment groups.

The results of the dose finding studies and arguments for the dose regimen chosen by the Applicant for the phase III studies were essentially accepted at the CHMP advice discussion although it was made clear that the evidence from the phase II trials was weak.

2.5.2. Main studies

The clinical development program consists of 3 studies, evaluating the treatment of acute VTE (one DVT study and one PE study), and one placebo-controlled study focussing on secondary prevention of VTE.

The PE study is still on-going and no data from that study is available for this report.

Thus, there are two phase III studies supporting the application as summarised in the table below.

Table E-2 Overview of completed clinical studies in phase III

Study number/ primary indication	Design	Rivaroxaban regimen and treatment duration	Comparator and treatment duration	Number of subjects randomized to rivaroxaban	Number of subjects randomized to comparator treatment
phase III trials					
11702 DVT acute symptomatic proximal DVT without symptomatic PE	multicenter, randomized, open-label, event-driven non-inferiority study for efficacy	15 mg b.i.d. for 3weeks followed by 20 mg o.d. 3, 6 or 12 months	enoxaparin b.i.d.overlapping with and followed by VKA 3, 6 or 12 months [b]	1731 R 1718 VFS 1731 ITT 1525 PP	1718 R 1711 VFS 1718 ITT 1571 PP
11899 continued treatment of VTE after 6 to 14 months of anticoagulant treatment	multicenter, randomized, double-blind, event-driven superiority study for efficacy	20 mg o.d. 6 or 12 months	placebo 6 or 12 months [b]	602 R 598 VFS 602 ITT 550 PP	595 R 590 VFS 594 ITT 554 PP

b.i.d.=twice daily; DVT = deep vein thrombosis; LMW= low molecular weight; ITT= intention to treat population; o.d.=once daily; PP=per protocol population R=randomized; VFS=valid for safety population; VKA=vitamin K antagonist [b] based on the risk profile of the subject, and local preferences, decision made by the investigator at the time of randomization

Note: In all studies, study outcomes were assessed by an independent central adjudication committee that was unaware of treatment allocation.

3.6.2.1 Pivotal study - study 11702

Methods/ Objectives

Study 11702, which is to be regarded as the pivotal study supporting this application, was a multi-center, randomized, open-label, parallel-group, active-controlled, event-driven non-inferiority study in patients with confirmed (by venography or CUS) proximal DVT without symptomatic PE. A treatment duration of 3, 6, or 12 months was to be decided by the investigators based on perceived risks.

It is to be noted that patients with estimated creatinine clearance < 30 ml/min or significant liver disease were excluded.

Treatments

Pre-randomization treatment with any anticoagulant was allowed for a maximum duration of 48 hours.

After randomization, subjects allocated to the rivaroxaban arm received rivaroxaban 15 mg twice daily for a total of 3 weeks followed by rivaroxaban 20 mg once daily. Subjects allocated to the comparator arm received enoxaparin twice daily for at least 5 days in combination with VKA and continued with VKA only after the INR had been ≥ 2 for two consecutive measurements at least 24 hours apart. Warfarin and acenocoumarol were allowed as VKAs.

Outcomes/endpoints

The primary efficacy objective was to evaluate whether rivaroxaban is at least as effective as enoxaparin/VKA in the treatment of DVT and secondary prevention of DVT and PE.

The principal safety objective was the evaluation of major and clinically relevant non-major bleeding.

The primary efficacy outcome was symptomatic recurrent VTE, i.e. the composite of recurrent DVT or non-fatal or fatal PE. All events should be objectively verified by CUS, venography, spiral CT, pulmonary angiography or lung scintigraphy. Fatal PE could also be verified at autopsy. Deaths which could not be attributed to documented cause and for which DVT/PE could not be ruled out was also counted as suspected PE.

The main secondary efficacy outcomes were recurrent DVT, non-fatal PE and all cause mortality (i.e. a composite outcome where in the primary efficacy outcome fatal PE was substituted by all cause mortality).

Thus the endpoints chosen are in line with the recommendations in the CHMP Note for Guidance document.

Sample size

The sample size was chosen to demonstrate that treatment with rivaroxaban is at least as effective as comparator treatment with enoxaparin/VKA. A total number of 88 events was determined to maintain a power of 90% to demonstrate that rivaroxaban is at least as effective as the comparator, considering a relative non-inferiority upper CI margin for the hazard ratio of 2.0.

Conduct of the study

Subjects in both treatment arms had contact with the site at fixed intervals. At each contact, all subjects were interviewed using a standardized outcome form for efficacy as well as for bleeding events. Recurrent VTE was more often suspected in the rivaroxaban arm and more events were refuted in that group by the adjudication committee. The reason for this was probably a closer supervision of the patients in the experimental arm by the investigators taking the open label design into account. However, the adjudication committee seems to have made the outcome assessment in a rigorous manner and it was made blinded.

Approximately 95% of the patients in the rivaroxaban group and 92% in the Enoxaparin/VKA group completed the intended treatment period or had a primary efficacy outcome or died, or the study was terminated after the required number of events was reached.

Baseline data

The baseline characteristics of the included patients are judged to be sufficiently representative of the European target population with 57% males and 43 % females, the mean age was 56 years and 13% were above 75 years of age, the mean weight was 82 kg. Seven percent of patients had moderate renal impairment.

Outcome data in patients with several risk factors were requested by the CHMP and such data have been provided and appropriate recommendations should be implemented in the SPC.

Results

Sixty-two percent of patients had spontaneous (idiopathic) DVT, 20% had recent surgery or trauma, another 15% had had immobilisation and six percent had use of estrogen containing drugs. Six % had active cancer.

The observed INR measurements within target are given in the table below.

Table E-3 Percentage of INR values within target range

Week 1	Week 2	Week 3	Week 4	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7
59 %	52%	57%	56%	59 %	62%	62%	63%	64%	64%
				Month 8	Month 9	Month 10	Month 11	Month 12	
				67%	66%	68%	65%	59%	

The proportion of observed INR within the target range among the VKA treated patients could be judged to be reasonably representative for what can be expected in clinical routine in a DVT population.

The incidence rates of the efficacy events were as follows:

Table E-4 Primary efficacy events, study 11702

Outcome/ components	Rivaroxaban N=1731 (100%)	Enox/VKA N=1718 (100%)
Primary efficacy outcome (pre-specified)	36 (2.1%)	51 (3.0%)
Death (PE)	1 (<0.1%)	0
Death (PE cannot be excluded)	3 (0.2%)	6 (0.3%)
Symptomatic PE and DVT	1 (<0.1%)	0
Symptomatic recurrent PE only	20 (1.2%)	18 (1.0%)
Symptomatic recurrent DVT only	14 (0.8%)	28 (1.6%)
Secondary efficacy outcome (pre-specified)	69 (4.0%)	87 (5.1%)
Death (PE)	1 (<0.1%)	0
Death (PE cannot be excluded)	3 (0.2%)	6 (0.3%)
Death (bleeding)	1 (<0.1%)	5 (0.3%)
Death (cardiovascular)	2 (0.1%)	4 (0.2%)
Death (other)	31 (1.8%)	34 (2.0%)
Symptomatic PE and DVT	1 (<0.1%)	0
Symptomatic recurrent PE only	20 (1.2%)	18 (1.0%)
Symptomatic recurrent DVT only	14 (0.8%)	28 (1.6%)
Recurrent DVT	14 (0.8%)	28 (1.6%)
Deep Vein Thrombosis, Proximal	13 (0.8%)	27 (1.6%)
Deep Vein Thrombosis, Distal	1 (<0.1%)	1 (<0.1%)

For the primary efficacy analysis, a Cox's proportional hazard model stratified for intended treatment duration and adjusted for baseline malignancy (yes/no) fitted for the primary efficacy outcome up to the end of the intended treatment period was employed. The comparison of rivaroxaban vs. enoxaparin/VKA treatment yielded a hazard ratio of 0.680 (95% confidence interval [CI]: 0.443-1.042). The test for superiority of rivaroxaban was not statistically significant (p = 0.0764).

Thus, the non-inferiority for rivaroxaban as pre-defined has been convincingly demonstrated. The results appear consistent for the components of the composite primary end-point. Recurrent non-fatal PE were numerically somewhat more common in the rivaroxaban group. However, this was probably due to chance and it is not expected that effective secondary prevention of DVT would not result in a similar reduction of PE events.

The efficacy results were essentially consistent in subgroups at centers with different time in therapeutic range (TTR). However, in centers with highest TTR (>70%) the tendency for better efficacy with rivaroxaban was lost.

The outcome in the Per Protocol population was consistent with that in the ITT population.

The Kaplan-Meier cumulative event probability rates for the primary efficacy end-point were numerically lower in the rivaroxaban group than in the enoxaparin/VKA group at each time point up to the end of intended treatment period except for the period up to Day 14. At day 7 there were 16 events in the rivaroxaban group versus 11 in the enoxaparin group and at day 14 21 vs 19, respectively. The slight numerical imbalance was judged to probably be due to chance.

It was noted that the majority of patients (73% in the rivaroxaban group) had received LMWH, heparin or fondaparinux before diagnostic procedures and before randomisation. This treatment is most probably not given by random but could be expected to be given to those with a high VTE suspicion or with more active disease.

The relative efficacy for rivaroxaban as compared to enoxaparin/VKA was consistent in different subgroups and in subgroups at different baseline risk. The relative difference between the treatment groups also appears consistent in different geographical regions. However the overall VTE rates differ in different geographical regions, which may be due to differences between the populations recruited.

A total of 446 suspected episodes of recurrent deep vein thrombosis or pulmonary embolism were identified by the investigators. The adjudication committee refuted the diagnosis of recurrent deep vein thrombosis or pulmonary embolism in 355 cases (193 cases in the rivaroxaban group and 162 cases in the enoxaparin/VKA group). A plausible explanation for the higher rate of investigator suspected events refuted centrally could be a higher alertness for these patients by the investigators taking the open label design into account. Other explanations have on request by the CHMP been discussed by the Applicant but appear less plausible.

The following table summarise the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Title: Oral direct factor Xa inhibitor rivaroxaban in patients with acute symptomatic deep vein thrombosis - The EINSTEIN DVT study			
Study identifier	011702 DVT		
Design	Multi-center, randomized, open-label, parallel-group, active-controlled, event-driven non-inferiority study; central independent adjudication committee for suspected clinical outcomes was blinded to treatment allocation		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		3, 6 or 12 months (determined by the investigator individually before randomization) No fixed run-in phase – the pre-randomization period of anticoagulant therapy could extend to a maximum of 48 hours Either patients were followed up for 30 days after end of their intended treatment or they were directly transferred into an extended treatment study protocol (Study 11899) and were to receive their study medication (rivaroxaban or placebo) for 6 or 12 months
Hypothesis	Non-inferiority		
Treatments groups	Overall study cohort		Rivaroxaban. 3 to 12 months treatment duration, 1731 patients randomized Enoxaparin/VKA. 3 to 12 months treatment duration, 1718 patients randomized
	3 months intended treatment duration		Rivaroxaban. 208 patients randomized Enoxaparin/VKA. 203 patients randomized
	6 months intended treatment duration		Rivaroxaban. 1083 patients randomized Enoxaparin/VKA. 1083 patients randomized
	12 months intended treatment duration		Rivaroxaban. 440 patients randomized Enoxaparin/VKA. 432 patients randomized
Endpoints and definitions	Primary outcome	Recurrent VTE	The composite of recurrent DVT or non-fatal or fatal PE
	Secondary outcome	Secondary efficacy outcome	The composite of recurrent DVT, non-fatal PE and all cause mortality

	Secondary outcome	Net clinical benefit 1	The composite of recurrent DVT or non-fatal or fatal PE (the primary efficacy outcome) and major bleeding events
	Secondary outcome	Net clinical benefit 2	The composite of recurrent DVT or non-fatal or fatal PE (the primary efficacy outcome), major bleeding events, CV deaths, MIs, strokes, and non-CNS systemic embolisms
	Other endpoint	Principal safety outcome	The composite of major bleeding events and clinically relevant non-major bleeding events
	Other endpoint	Major bleeding events	Incidence of major bleeding events
	Other endpoint	Fatal bleeding events	Incidence of major bleeding events associated with fatal outcome
	Other endpoint	Non- fatal major bleeding events in a critical site	Incidence of major bleeding events in a critical site (intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal)
	Other endpoint	Major bleeding event: non-fatal non critical organ bleeding	Incidence of major bleeding events occurring as overt bleeding associated with transfusion of 2 or more units of packed red blood cells or whole blood and/or associated with a decrease in hemoglobin of 2 g/dL or more
	Other endpoint	Intracranial haemorrhage	Incidence of intracranial haemorrhage
	Other endpoint	All-cause mortality	Incidences of deaths
	Other endpoint	Vascular events	Incidence of vascular events
Database lock	26 Jul 2010		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat All confirmed efficacy outcomes up to the end of the intended duration of treatment irrespective of the actual treatment duration - time to the first event of the composite efficacy outcome (Cox's proportional hazard model for rivaroxaban vs. enox/VKA)			
Descriptive statistics and estimate variability	Treatment group	Rivaroxaban	Enoxaparin/VKA	
	Number of subjects	1731	1718	
	Primary efficacy outcome (composite of recurrent DVT or non-fatal or fatal PE)	Incidence rate: 2.1%	Incidence rate: 3.0%	
Analysis description	**Secondary Analyses**			
Descriptive statistics and estimate variability	Treatment group	Rivaroxaban	Enoxaparin/VKA	
	Number of subjects	1731	1718	

	Secondary efficacy outcome	Incidence rate: 4.0%	Incidence rate: 5.1%	
	Net clinical benefit 1	Incidence rate: 2.9%	Incidence rate: 4.2%	
	Net clinical benefit 2	Incidence rate: 3.6%	Incidence rate: 4.7%	
Analysis description	**Safety Analyses**			
Descriptive statistics and estimate variability	Treatment group	Rivaroxaban	Enoxaparin/VKA	
	Number of subjects	1718	1711	
	Principal safety outcome (composite of major bleeding events and clinically relevant non-major bleeding events)	Incidence rate: 8.1%	Incidence rate: 8.1%	
	Major bleeding events	Incidence rate: 0.8%	Incidence rate: 1.2%	
	Fatal bleeding events	Incidence rate: <0.1%	Incidence rate: 0.3%	
	Non-fatal major bleeding events in a critical site	Incidence rate: 0.2%	Incidence rate: 0.2%	
	Major bleeding event: non-fatal non critical organ bleeding	Incidence rate: 0.6%	Incidence rate: 0.7%	
	Intracranial haemorrhage	Incidence rate: 0.1%	Incidence rate: 0.1%	
	All-cause mortality	Incidence rate: 2.4%	Incidence rate: 3.0%	
	Vascular events	Incidence rate: 0.7%	Incidence rate: 0.8%	

Effect estimate per comparison	Primary efficacy outcome (composite of recurrent DVT or non-fatal or fatal PE)	Comparison groups	Rivaroxaban vs. enoxaparin/VKA
		Hazard ratio	0.680
		95% confidence interval	0.443 – 1.042
		P-value, non-inferiority P-value, superiority	P < 0.0001 P =0.0764
	Secondary efficacy outcome (recurrent DVT, non-fatal PE and all cause mortality)	Comparison groups	Rivaroxaban vs. enoxaparin/VKA
		Hazard ratio	0.722
		95% confidence interval	0.526 -0.991
		Nominal P-value, superiority	P = 0.0436
	Net clinical benefit 1 (primary efficacy outcome and	Comparison groups	Rivaroxaban vs. enoxaparin/VKA
		Hazard ratio	0.667

	major bleeding events)	95% confidence interval	0.466 -0.954
		Nominal P-value, superiority	P = 0.0265
	Net clinical benefit 2 (the primary efficacy outcome plus major bleeding events, CV deaths, MIs, strokes, and non-CNS systemic embolisms	Comparison groups	Rivaroxaban vs. enoxaparin/VKA
		Hazard ratio	0.727
		95% confidence interval	0.522 -1.013
		Nominal P-value, superiority	P = 0.0594
	Principal safety outcome (composite of major bleeding events and clinically relevant non-major bleeding events)	Comparison groups	Rivaroxaban vs. enoxaparin/VKA
		Hazard ratio	0.966
		95% confidence interval	0.763 -1.222
		P-value for superiority	P = 0.7709
	Major bleeding events	Comparison groups	Rivaroxaban vs. enoxaparin/VKA
		Hazard ratio	0.646
		95% confidence interval	0.326 -1.282
		P-value for superiority	P = 0.2117
Notes	All cause mortality is based on any post-randomization death. otherwise safety variables are presented as treatment emergent.		
Analysis description	For the primary efficacy analysis, the time to the first event of the composite primary efficacy outcome was analyzed using a Cox's proportional hazards model, with intended treatment duration as stratum and adjusted for the baseline presence of malignancy. The rivaroxaban-to-comparator hazard ratio was computed with two-sided 95% confidence intervals (CIs). Based on this model, rivaroxaban was to be considered at least as effective as the comparator if the upper limit of the CI was less than 2.0. To account for multiple testing, a hierarchical testing procedure was pre-specified, and comprised non-inferiority and superiority testing for the primary efficacy outcome. Furthermore, if non-inferiority for the primary efficacy outcome was demonstrated, the principal safety outcome (composite of major and clinically relevant non-major bleeding events), as well as the major bleeding outcome were to be tested hierarchically. Secondary efficacy outcomes were not included in the hierarchical testing procedure.		

3.6.2.2 Supportive study – study 11899

Methods/ Objectives

Study 11899 was a multicenter, randomized, double-blind, placebo-controlled, event-driven, superiority study for efficacy. Subjects with a previous confirmed symptomatic DVT or PE who either had been treated for 6 or 12 months with vitamin K antagonists (VKA) or rivaroxaban in study 11702 **or** who had been treated for 6 to 14 months with VKA (either warfarin or acenocoumarol) outside of study 11702 were eligible for this trial.

After randomization, subjects allocated to rivaroxaban received rivaroxaban 20 mg once daily. Subjects allocated to placebo received a matching placebo tablet once daily. The treatment duration was indicated prior to randomization (6 or 12 months) at the investigator's discretion.

Outcome/Endpoints

The primary efficacy outcome was the composite of confirmed recurrent DVT or non-fatal or fatal PE.

The study was designed as an event-driven superiority study where all events were evaluated by a central, blinded, independent adjudication committee.

Baseline Characteristics

The demographics, baseline characteristics and risk factors were similar to the study population in study 11702 from which 53% of the included patients were recruited.

Conduct of the study

Twenty six (26) % of the patients did not complete the planned treatment duration as the Sponsor terminated the study when the pre-planned number of events had been reached. Another 14 % had shorter treatment duration for other reasons (adverse events 6.5 vs 3.1% in the rivaroxaban and placebo groups, respectively) or due to primary end-point reached (1.0% vs 8.5%, respectively) or for other reasons.

Results

Efficacy data in relation to number of risk factors and in relation to compliance to treatment were consistent. More bleedings were noted in patients with poorer treatment compliance in the rivaroxaban group which was probably due to more frequent interruptions of treatment in that group when a bleeding occurred.

As primary analysis, a Cox's proportional hazard model stratified for planned treatment duration and adjusted for previous treatment was applied. The comparison of rivaroxaban vs. placebo treatment yielded a hazard ratio of 0.185 (95% CI 0.087-0.393, $p < 0.0001$) or a 81% relative risk reduction. A pre-planned hierarchy for statistical testing of the three secondary efficacy outcomes was applied in the order of secondary efficacy outcome 1 to 3, (see table below for definitions and outcome). The differences between the two treatment groups were highly statistically significant for all three secondary efficacy endpoints.

Table E-5 Efficacy outcome, study 11899

Variable/ components	Rivaroxaban 20 mg o.d. N=602 (100%)	Placebo N=594 (100%)
Primary efficacy outcome	8 (1.3%)	42 (7.1%)
Death (PE)	0	1 (0.2%)
Death (PE cannot be excluded)	1 (0.2%)	0
Symptomatic recurrent PE	2 (0.3%)	13 (2.2%)
Symptomatic recurrent DVT	5 (0.8%)	31 (5.2%)
Secondary efficacy outcome 1	8 (1.3%)	43 (7.2%)
Death (PE)	0	1 (0.2%)
Death (PE cannot be excluded)	1 (0.2%)	0
Death (other)	0	1 (0.2%)
Symptomatic recurrent PE	2 (0.3%)	13 (2.2%)
Symptomatic recurrent DVT	5 (0.8%)	31 (5.2%)
Secondary efficacy outcome 2	9 (1.5%)	44 (7.4%)
Death (PE)	0	1 (0.2%)
Death (PE cannot be excluded)	1 (0.2%)	0
Death (other)	0	1 (0.2%)
Symptomatic recurrent PE	2 (0.3%)	13 (2.2%)
Symptomatic recurrent DVT	5 (0.8%)	31 (5.2%)
STEMI	1 (0.2%)	0
Ischemic Stroke	0	1 (0.2%)
Secondary efficacy outcome 3	12 (2.0%)	42 (7.1%)
Death (PE)	0	1 (0.2%)
Death (PE cannot be excluded)	1 (0.2%)	0
Symptomatic recurrent PE	2 (0.3%)	13 (2.2%)
Symptomatic recurrent DVT	5 (0.8%)	31 (5.2%)
Major bleeding	4 (0.7%)	0
Recurrent VTE (PE or DVT)	7 (1.2%)	42 (7.1%)
Symptomatic recurrent PE	2 (0.3%)	13 (2.2%)
Symptomatic recurrent DVT	5 (0.8%)	31 (5.2%)
Recurrent DVT	5 (0.8%)	31 (5.2%)
Deep vein thrombosis, proximal	5 (0.8%)	31 (5.2%)
Deep vein thrombosis, distal	0	5 (0.8%)

The study provided clear evidence for the efficacy of rivaroxaban in the secondary prevention after VTE. The net clinical benefit endpoints combining efficacy and safety endpoints appeared less informative as putting equal weight on these different endpoints could be questioned.

The implications for treatment in clinical routine from this study are less obvious.

The size of the efficacy is to a large extent dependant on how patients are selected. The study included patients at rather different risk. Approximately sixty percent had had an idiopathic DVT/PE, 16% had had more than one DVT/PE event, 14 % had had a primary event during immobilisation, 8% had a known thrombophilic condition and 5% had active cancer. Thus it is questionable to what extent the population is representative for a population where treatment generally is discontinued (as in the placebo group) or continued for 6 or 12 additional months (as in the rivaroxaban group) or without any predefined discontinuation time point. Furthermore no comparison with continued VKA treatment was performed. It does not seem plausible however that VKA treatment would have provided much

additional benefit. Another interesting aspect of the results is the possibility to compare the safety characteristics of rivaroxaban with placebo in the target population.

2.5.3. Discussion on clinical efficacy

With regard to efficacy this application is essentially supported by the results from one pivotal study (11702). Based on the results from this study the Applicant proposed a new treatment strategy of acute proximal DVT with rivaroxaban that substitutes well established regimens with initial parenteral therapy followed by VKA treatment for secondary prophylaxis that has been in practice for more than fifty years.

Study 11702 is judged to have been well designed and well performed. The efficacy events were centrally adjudicated while blinded. The composite primary end-point (recurrent DVT or non-fatal or fatal PE) and prioritised secondary endpoint are in line with the CHMP guidance document and the CHMP considered that they can be accepted. Non inferiority of the composite primary and secondary endpoints has been convincingly demonstrated with a with a hazard ratio of 0.68 (95% CI 0.44-1.04, $p<0.0001$ for non-inferiority). Superiority could however not be demonstrated ($p=0.076$). In addition, the results appear consistent for different subgroups and the evidence provided by secondary endpoints is supportive.

Study 11899 was randomized, event-driven, superiority study for efficacy. Although double-blind and placebo-controlled it is considered to be primarily supportive from an efficacy point of view since it was performed in a population that was not considered to necessarily be in need of prolonged anticoagulant treatment.

The outcome of the trial was heavily influenced by the selection of patients into the study which probably would vary considerably between different investigators. Nevertheless superiority over placebo was considered by the CHMP to be convincingly demonstrated and thus that rivaroxaban is effective in the secondary prevention of VTE is considered established. The study also provided evidence for efficacy with regard to secondary prevention of pulmonary embolism.

The study did not compare the efficacy with VKA treatment which would be the alternative for the majority of patients. However, the low event rates observed in the actively treated arm would be expected also with VKA treatment in a population without malignant disease,

Efficacy data from centers with different quality of the VKA treatment measured as proportion of patients within the target range were consistent with the overall outcome.

A majority of patients received LMWH, heparin or fondaparinux for up to 48 hours before rivaroxaban treatment was started. It is, however, agreed with the Applicant that there is little evidence that supports a general recommendation for the use of parenteral anticoagulants in the initial phase of acute treatment. The similar time of onset after administration of the two anticoagulants is of vital importance for this conclusion.

Furthermore, the lack of experience of treatment beyond one year needs to be appropriately addressed and was further discussed and considered in the product information and in the risk management plan.

2.5.4. Conclusions on the clinical efficacy

Rivaroxaban could be an attractive alternative to VKA treatment which often requires intense monitoring and is complicated by numerous drug interactions. From this practical perspective treatment with rivaroxaban probably offers some advantages.

2.6. Clinical safety

Patient exposure

The exposure in the phase II and III trials within this indication can be summarised in the following tables.

Number of subjects valid for safety in the dose finding studies (by daily dose) (studies 11223 and 11528)

Table S-1 Number of patients valid for safety in the phase II trials

Drug and Dosage Level (total daily dose)	N
Rivaroxaban 20 mg	254
Rivaroxaban 30 mg	134
Rivaroxaban 40 mg	374
Rivaroxaban 60 mg	121
Total number of rivaroxaban subjects	883
Heparin/VKA	263

Table S-2 Duration of actual study treatment - pool of study 11702 DVT and 11899 - subjects valid for safety with rivaroxaban treatment

Total treatment duration categories (cumulative)	Rivaroxaban treated subjects n (%)
n (non-missing)	2191 (100.0%)
≥ 1 day	2191 (100.0%)
≥ 1 month	2104 (96.0%)
≥ 3 months (91 days)	2026 (92.5%)
≥ 6 months (178 days)	1660 (75.8%)
≥ 9 months (268 days)	521 (23.8%)
≥ 12 months (352 days)	427 (19.5%)
≥ 15 months (442 days)	29 (1.3%)
≥ 18 months (530 days)	16 (0.7%)
≥ 21 months (620 days)	3 (0.1%)
≥ 24 months (704 days)	0

Thus, the safety database contains approximately 3000 patients included in the phase II and III studies of which more than 400 patients have been treated for over 12 months which is considered acceptable for approval.

The demographic profile of the patients valid for safety analysis in the phase III trials is given in the table below.

Table S-3 Demographic profile of the patients valid for safety analysis in the phase III trials

	Study 11702 DVT		Study 11899	
Demographic variable	Rivaroxaban 20 mg o.d.[b] (N=1718)	Enox/VKA (N=1711)	Rivaroxaban 20 mg o.d. (N=598)	Placebo (N=590)
Sex, n (%)				
Male	987 (57.5%)	963 (56.3%)	351 (58.7%)	338 (57.3%)
Female	731 (42.5%)	748 (43.7%)	247 (41.3%)	252 (42.7%)
Race				
White	1316 (76.6%)	1315 (76.9%)	464 (77.6%)	459 (77.8%)
Black	38 (2.2%)	43 (2.5%)	16 (2.7%)	13 (2.2%)
Asian	227 (13.2%)	217 (12.7%)	47 (7.9%)	48 (8.1%)
American Indian or Alaska native	1 (<0.1%)	2 (0.1%)	1 (0.2%)	1 (0.2%)
Hispanic	9 (0.5%)	9 (0.5%)	1 (0.2%)	2 (0.3%)
Uncodeable	5 (0.3%)	2 (0.1%)	1 (0.2%)	2 (0.3%)
N/A[a]	122 (7.1%)	123 (7.2%)	68 (11.4%)	65 (11.0%)
Calculated age at enrollment				
Mean ± SD	55.8 ± 16.5	56.4 ± 16.3	58.2 ± 15.6	58.4 ± 16.0
Age groups				
18 - 40 years	334 (19.4%)	312 (18.2%)	86 (14.4%)	94 (15.9%)
>40 - <65 years	800 (46.6%)	795 (46.5%)	272 (45.5%)	279 (47.3%)
65 - 75 years	369 (21.5%)	381 (22.3%)	152 (25.4%)	119 (20.2%)
>75 years	215 (12.5%)	223 (13.0%)	88 (14.7%)	98 (16.6%)
Weight (kg)				
Mean ± SD	82.1 ± 18.4	81.6 ± 18.9	83.9 ± 17.9	82.9 ± 17.7
Body Mass Index (kg/m2)				
Mean ± SD	27.8 ± 5.4	27.8 ± 5.5	28.5 ± 5.5	28.2 ± 5.0
BMI Group				
< 18.5 kg/m²	21 (1.2%)	24 (1.4%)	3 (0.5%)	5 (0.8%)
18.5 - < 25 kg/m²	520 (30.3%)	539 (31.5%)	141 (23.6%)	137 (23.2%)
25 - < 30 kg/m²	657 (38.2%)	657 (38.4%)	251 (42.0%)	252 (42.7%)
30 - < 35 kg/m²	354 (20.6%)	312 (18.2%)	122 (20.4%)	137 (23.2%)
35 - < 40 kg/m²	103 (6.0%)	121 (7.1%)	42 (7.0%)	31 (5.3%)
≥ 40 kg/m²	51 (3.0%)	49 (2.9%)	22 (3.7%)	14 (2.4%)
Creatinine clearance				
< 30 mL/min	6 (0.3%)	9 (0.5%)	0	5 (0.8%)
30 - < 50 mL/min	114 (6.6%)	119 (7.0%)	37 (6.2%)	44 (7.5%)
50 - < 80 mL/min	390 (22.7%)	400 (23.4%)	133 (22.2%)	121 (20.5%)
≥ 80 mL/min	1186 (69.0%)	1166 (68.1%)	371 (62.0%)	371 (62.9%)

Approximately 46 % of the subjects were recruited in West European countries, 15% from Eastern Europe, 11% from Asia, 8% from North America and 21% from other areas (Australia, Brazil, Israel, New Zealand and South Africa).

Risk factors thromboembolism for recurrent VTE were similar in both studies. Idiopathic DVT/PE was the most frequent one (in the range of 50% in study 11702 DVT and 60% in study 11899), followed by previous episodes of DVT/PE (in the range of 20% in study 11702 DVT and 15% in study 11899) and immobilisation (in the range of 15% in both studies).

Almost half of the subjects from study 11702 DVT and 11899 had vascular disorders, mainly related to hypertensive disease. Other medical history findings fit into the cardiovascular disease and risk factor profile such as diabetes mellitus (12%), ischemic coronary artery disorders (5%) and lipid

abnormalities. The profile of medical history findings is probably rather typical for subjects prone to develop VTE.

In accordance with the medical findings more than 50% of subjects received drugs for the cardiovascular system, primarily antihypertensive treatment. The use of serum lipid reducing agents and drugs acting on the musculo-skeletal system is also explained by the co-morbidities. Approximately 7 % were on ASA and 9% on NSAID at baseline.

Adverse events

A summary of the most common treatment-emergent adverse events (at least 2% in any treatment group) by MedDRA system organ class/preferred term is given in the table below.

Table S-4 Treatment emergent events in the phase III studies

MedDRA SOC Preferred term (primary term)	Study 11702 DVT Rivaroxaban 20 mg o.d.[a] (N=1718)	 Enox/VKA (N=1711)	Study 11899 Rivaroxaban 20 mg o.d. (N=598)	 Placebo (N=590)
ANY EVENT	1078 (62.7%)	1080 (63.1%)	335 (56.0%)	325 (55.1%)
Gastrointestinal disorders				
Constipation	48 (2.8%)	43 (2.5%)	6 (1.0%)	5 (0.8%)
Diarrhoea	54 (3.1%)	40 (2.3%)	7 (1.2%)	8 (1.4%)
Gingival bleeding	36 (2.1%)	28 (1.6%)	11 (1.8%)	2 (0.3%)
Nausea	47 (2.7%)	38 (2.2%)	7 (1.2%)	6 (1.0%)
Rectal haemorrhage	36 (2.1%)	19 (1.1%)	4 (0.7%)	4 (0.7%)
General disorders and administration site conditions				
Chest pain	36 (2.1%)	31 (1.8%)	16 (2.7%)	15 (2.5%)
Oedema peripheral	41 (2.4%)	41 (2.4%)	13 (2.2%)	17 (2.9%)
Pyrexia	43 (2.5%)	38 (2.2%)	5 (0.8%)	7 (1.2%)
Infections and infestations				
Bronchitis	24 (1.4%)	34 (2.0%)	11 (1.8%)	17 (2.9%)
Influenza	38 (2.2%)	38 (2.2%)	11 (1.8%)	12 (2.0%)
Nasopharyngitis	93 (5.4%)	84 (4.9%)	31 (5.2%)	30 (5.1%)
Urinary tract infection	37 (2.2%)	32 (1.9%)	7 (1.2%)	3 (0.5%)
Injury, poisoning and procedural complications				
Contusion	53 (3.1%)	68 (4.0%)	19 (3.2%)	16 (2.7%)
Investigations				
ALT increased	20 (1.2%)	52 (3.0%)	2 (0.3%)	4 (0.7%)
INR increased	1 (<0.1%)	38 (2.2%)	0	0
Musculoskeletal and connective tissue disorders				
Arthralgia	43 (2.5%)	38 (2.2%)	20 (3.3%)	21 (3.6%)
Back pain	50 (2.9%)	31 (1.8%)	22 (3.7%)	7 (1.2%)
Pain in extremity	76 (4.4%)	66 (3.9%)	29 (4.8%)	35 (5.9%)
Nervous system disorders				
Dizziness	38 (2.2%)	22 (1.3%)	6 (1.0%)	8 (1.4%)
Headache	91 (5.3%)	68 (4.0%)	18 (3.0%)	15 (2.5%)
Renal and urinary disorders				
Haematuria	39 (2.3%)	41 (2.4%)	13 (2.2%)	2 (0.3%)
Reproductive system and breast disorders				
Menorrhagia	49 (2.9%)	19 (1.1%)	5 (0.8%)	2 (0.3%)
Respiratory, thoracic and mediastinal disorders				
Cough	72 (4.2%)	51 (3.0%)	16 (2.7%)	21 (3.6%)
Dyspnoea	33 (1.9%)	37 (2.2%)	7 (1.2%)	11 (1.9%)
Epistaxis	89 (5.2%)	74 (4.3%)	24 (4.0%)	11 (1.9%)
Vascular disorders				
Haematoma	37 (2.2%)	59 (3.4%)	7 (1.2%)	8 (1.4%)
Hypertension	38 (2.2%)	40 (2.3%)	6 (1.0%)	9 (1.5%)

a 15 mg b.i.d. for 3 weeks, followed by 20 mg o.d.

Overall, the incidence of treatment-emergent *drug-related* AEs was in the range of 20% in the rivaroxaban treatment groups (study 11702 DVT: 23.3% rivaroxaban treatment group vs. 23.0% enoxaparin/VKA; study 11899: 16.4% rivaroxaban treatment group vs. 10.7% placebo). The difference between the rivaroxaban treatment group and the placebo group is driven by investigator reported bleeding events (incidence of treatment-emergent drug-related bleeding events in study 11899: 11.0% rivaroxaban treatment group vs. 6.3% placebo group). The incidence of treatment-emergent drug-related AEs without bleeding events in study 11899 was 7.0% rivaroxaban treatment group vs. 6.1% placebo group.

The only marked differences from placebo in study 11899 are the higher incidences of gingival bleeding and epistaxis in the rivaroxaban group.

Overall, the incidence of *drug-related serious* TEAEs was in the range of 2% in the rivaroxaban treatment groups (study 11702 DVT: 2.4% rivaroxaban treatment group vs. 3.0% enoxaparin/VKA; study 11899: 2.0% rivaroxaban treatment group vs. 0.8% placebo). The incidences of adverse events resulting in permanent discontinuation of study drug were similar in the two treatment groups in study 11702.

The most frequently reported drug-related serious TEAEs in study 11702 DVT were: Rivaroxaban treatment group: anemia (0.6%), all other preferred terms had an incidence of < 3 reports

Serious adverse event/deaths/other significant events

In the safety population, 93 subjects died within the study period until last observation made. The incidence rate of death was numerically lower in the rivaroxaban group (2.4% [41/1718]) than in the enoxaparin/VKA group (3.0% [52/1711]). The numerical difference in death rates between treatment groups until last observation in favour of rivaroxaban may have been due to chance. As judged from the case reports other causes of death than VTE, bleeding or treatment related complications seem established or probable in the majority of cases.

Bleedings

The criteria for major bleeding and clinically relevant bleeding seem appropriate and are essentially in line with the recommendations in the relevant CHMP NfG document. They were prospectively defined as follows

A major bleeding event was defined as overt bleeding

- associated with a fall in hemoglobin of 2 g/dL or more or
- leading to a transfusion of 2 or more units of packed red blood cells or whole blood or
- that occurred in a critical site: intracranial, intraspinal, intraocular, pericardial, intra articular, intramuscular with compartment syndrome, retroperitoneal or contributing to death.

Clinically relevant non-major bleeding events were defined as overt bleeding not meeting the criteria for major bleeding event but associated with

- medical intervention or
- unscheduled contact (visit or telephone call) with a physician or
- (temporary) cessation of study treatment or
- discomfort for the subject such as pain or
- impairment of activities of daily life

The numbers and distribution of major bleedings and clinically relevant bleedings in study 11702 are given in the two tables below.

Table S-5 All confirmed treatment-emergent major bleeding events (safety population of study 11702 DVT)

Bleeding event	Rivaroxaban (N=1718) n (%)	Enox/VKA (N=1711) n (%)
Major bleeding event	14 (0.8%)	20 (1.2%)
Fatal bleeding	1 (<0.1%)	5 (0.3%)
Intracranial	0	2 (0.1%)
Gastrointestinal	1 (<0.1%)	2 (0.1%)
Thorax	0	1 (<0.1%)
Non-fatal critical organ bleed	3 (0.2%)	3 (0.2%)
Intracranial	2 (0.1%)	0
Retroperitoneal	0	1 (<0.1%)
Intra-articular	0	1 (<0.1%)
Ocular		
Intraocular	1 (<0.1%)	0
Vitreous body	0	1 (<0.1%)
Non-fatal non-critical organ bleeding (fall in Hb ≥ 2 g/dl and/or transfusions ≥ 2 units)	10 (0.6%)	12 (0.7%)
Skin (other than injection site)	0	2 (0.1%)
Urogenital	1 (<0.1%)	3 (0.2%)
Uterus	5 (0.3%)	0
Gastrointestinal	3 (0.2%)	4 (0.2%)
Rectal	1 (<0.1%)	3 (0.2%)
Intramuscular	1 (<0.1%)	0

Note: Incidences are based on the number of subjects, not the number of events. Although a subject may have had 2 or more events, the subject is counted only once in a category. The same subject may appear in different categories.

Table S-6 All confirmed treatment-emergent clinically relevant non-major bleeding events (safety population of study 11702 DVT)

Safety outcome/ components	Rivaroxaban (N=1718) n (%)	Enox/VKA (N=1711) n (%)
Clinically relevant non-major bleeding	129 (7.5%)	122 (7.1%)
Surgical site	1 (<0.1%)	2 (0.1%)
Skin (other than injection site)	11 (0.6%)	28 (1.6%)
Urogenital	35 (2.0%)	29 (1.7%)
Uterus	29 (1.7%)	16 (0.9%)
Gingival	0	5 (0.3%)
Gastrointestinal	11 (0.6%)	14 (0.8%)
Rectal	22 (1.3%)	10 (0.6%)
Anal	1 (<0.1%)	0
Nasal	15 (0.9%)	15 (0.9%)
Tracheal	6 (0.3%)	0
Pharynx	0	1 (<0.1%)
Intra-articular	0	1 (<0.1%)
Conjunctival	1 (<0.1%)	3 (0.2%)
Intraocular	1 (<0.1%)	0
Ear	1 (<0.1%)	2 (0.1%)
Intramuscular	2 (0.1%)	3 (0.2%)
Leg	0	1 (<0.1%)
Indeterminate	1 (<0.1%)	0

Notes: Incidences are based on the number of subjects, not the number of events. Although a subject may have had 2 or more events, the subject is counted only once in a category. The same subject may appear in different categories. Percentages calculated with the number of subjects in each group as denominator. Treatment-emergent was defined as occurring after randomization and up to 2 days after the last dose of study drug.

Rectal, urogenital bleeding and bleedings from uterus that were judged as clinically relevant were numerically more common in the rivaroxaban group. Major and clinically relevant bleedings were slightly higher in the rivaroxaban group during the first 3 months of treatment (6.4 vs 5.8%, respectively). However, the differences in total number between the groups were small.

In study 11702 a total of 433/1718 (25.2%) subjects in the rivaroxaban treatment group and 399/1711 (23.3%) subjects in the enoxaparin/VKA treatment group had investigator-assessed, treatment-emergent bleeding events, most of them were assessed by the investigators as drug-related.

The totality of bleeding data, including also mild or trivial bleedings seem to indicate that bleeding was somewhat more common in the rivaroxaban treated patients as compared to enoxaparin/VKA treated. A total of 433/1718 (25.2%) subjects in the rivaroxaban treatment group and 399/1711 (23.3%) subjects in the enoxaparin/VKA treatment group had investigator-assessed, treatment-emergent bleeding events, most of them were assessed by the investigators as drug-related. However the incidences of major bleedings did not differ which to some extent is reassuring. The pattern of bleedings during rivaroxaban treatment seems to differ from what is seen during enoxaparin treatment with more bleedings from gastrointestinal tract and uterine bleedings, e.g for investigator reported uterus/urogenital bleedings a more marked difference is seen between the treatment groups in study 11702 with 88 bleedings in the rivaroxaban group vs. 38 in the enoxaparin/VKA group in female subjects below the age of 55.

Haemoglobin or haematocrit levels were not monitored during the studies. Thus the possibilities to detect clinically silent GI bleedings were limited.

As expected the bleeding incidence was clearly higher in the rivaroxaban group as compared to placebo in study 11899, see table below.

Table S-7 Bleedings in study 11899

Endpoint/ components	Rivaroxaban 20 mg o.d. (N=598) n (%)	Placebo (N=590) n (%)
Any bleeding event	104 (17.4%)	63 (10.7%)
Any major or clinically relevant non-major bleeding event	36 (6.0%)	7 (1.2%)
Major bleeding event	4 (0.7%)	0
Fall in hemoglobin ≥ 2 g/dL	4 (0.7%)	0
Transfusions ≥ 2 units	2 (0.3%)	0
Any clinically relevant non-major bleeding event	32 (5.4%)	7 (1.2%)
Surgical site	1 (0.2%)	0
Skin (other than injection site)	4 (0.7%)	2 (0.3%)
Urogenital	9 (1.5%)	0
Gastrointestinal	1 (0.2%)	0
Nasal	8 (1.3%)	1 (0.2%)
Rectal	6 (1.0%)	2 (0.3%)
Ear	1 (0.2%)	0
Uterus	3 (0.5%)	2 (0.3%)
Anal	1 (0.2%)	0
Any non major bleeding event (clinically relevant or not)	101 (16.9%)	63 (10.7%)
Any trivial bleeding event	75 (12.5%)	56 (9.5%)
Trivial bleeding events occurring in at least 1% of subjects (any treatment group)		
Skin (other than injection site)	37 (6.2%)	37 (6.3%)
Gingival	12 (2.0%)	3 (0.5%)
Nasal	17 (2.8%)	10 (1.7%)
Conjunctival	8 (1.3%)	0
Uterus	5 (0.8%)	6 (1.0%)

Looking at bleeding rates in subgroups it can be noted that the bleeding rates in patients with moderate renal insufficiency was increased (10.8%) as compared with patients with normal renal function (7.5%) and also somewhat higher in the rivaroxaban group as compared to the corresponding enoxaparin/VKA group (7.8%). In a parallel application for rivaroxaban treatment in atrial fibrillation the Applicant proposes a dose of 15 mg o.d. in patients with moderately impaired renal function. A dose of 15 mg will provide an exposure that is closer to the exposure of 20 mg in patients with no or mild renal impairment.

The reported analyses do not indicate that there was a difference in PT Neoplastin values in patients with bleedings and those without bleedings.

Hepatic adverse events

Overall, in study 11702 0.4% (7/1718) of the subjects in the rivaroxaban treatment group had hepatic disorder AEs resulting in permanent discontinuation of study drug compared with 0.4% (6/1711) subjects in the enoxaparin/VKA treatment group. There were no cases of acute hepatic failure in the rivaroxaban treated group. The incidence of ALT elevations were clearly lower in the rivaroxaban group than in the enoxaparin AKV group (E.g. >3ULN, 1.5 vs.3.8%).

The available data so far data does not indicate that treatment with rivaroxaban is associated with severe hepatic adverse events.

There were no indication that rivaroxaban induced ischemic vascular complications, thrombocytopenia or pancreatic adverse events.

2.6.1. Discussion on clinical safety

The safety database contains almost 3000 patients included in the phase II and III studies of which more than 400 patients have been treated for over 12 months. From a safety perspective it is considered valuable that the supportive study 11899 provides data in comparison with placebo. Thus the experience should be sufficient to capture common adverse events and to characterise bleeding risks in the target population. The reported incidence of major bleedings was not increased as compared to enoxaparin/VKA treatment. However, taking all available bleeding data including bleedings judged as clinically relevant, mild bleedings and investigator reported bleedings into account the incidence of bleedings seem to be somewhat higher among the rivaroxaban treated patients. The bleeding pattern seems to differ from what is seen during VKA treatment with a higher incidence of mucosal bleedings. The bleeding pattern has been discussed by the Applicant who claimed that there are similarities in the bleeding pattern with what can be seen in inherited fX deficiency. It appears, however, reassuring that major or critical bleedings were not more common than with VKA treatment in the overall clinical study programme. With the applied study design in the pivotal study occult GI bleedings were not systematically screened for. As anaemia was somewhat more common in the rivaroxaban group appropriate recommendations for clinical and laboratory monitoring should be included in the product information. The dose proposed in moderate renal impairment is questioned as the non-adjusted dose proposed will provide increased exposure and a dose reduction should be recommended.

There are currently no signals from the studies in the proposed new indication that treatment with rivaroxaban would be associated with severe hepatic adverse events, thrombocytopenia or pancreatic adverse reactions. The post-marketing experience from prophylaxis of VTE in orthopaedic surgery has so far not revealed any safety concerns resulting in regulatory actions.

2.6.2. Conclusions on the clinical safety

The safety characteristics of rivaroxaban in the targeted population have essentially been sufficiently characterised.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considers that the Pharmacovigilance system (version 10.0) as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

Risk Management Plan

The information provided below in the RMP refers to both DVT and SPAF indications undergoing parallel review and adopted simultaneously by the CHMP.

The applicant 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 • Modified Prescription event monitoring study • Drug utilisation database studies • Post-marketing non-interventional cohort studies in the VTE prevention population (XA0801; XAMOS study 13802), the SPAF population (XA1101; study 15914) and the VTE treatment population (XA1102; study 15915) • Prescriber/patient surveys will be performed in order to measure effectiveness of additional risk minimisation activities	• Contraindication in SmPC section 4.3 *"Contraindication"* • Warning in SmPC section 4.4 *"Special warnings and precautions for use"* • Warning in SmPC section 4.5 *"Interaction with other medicinal products and other forms of interactions"* *CYP3A4 and P-gp inhibitors* *Anticoagulants* *NSAIDs/platelet aggregation inhibitors* *Warfarin* • Haemorrhage is listed in the SmPC section 4.8 *"Undesirable effects"* • <u>For VTE treatment and SPAF indication</u> Additional risk minimisation activities: • Prescriber guide • Patient alert card
Important potential risks		
Increase in LFTs, bilirubin	• Routine pharmacovigilance activities • Additional information from ongoing trials • Post-marketing non-interventional cohort studies (XA0801; XAMOS study 13802, XA1101; study 15914 and XA1102; study 15915) <u>VTE treatment and SPAF indication</u> • Drug utilisation database studies	Elevated liver enzymes/bilirubin are listed in the SmPC section 4.8.

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Embryo-foetal toxicity	• Routine pharmacovigilance activities • Modified Prescription event monitoring study • Drug utilisation database studies • Post marketing non-interventional cohort studies (XA1101; study 15914 and XA1102; study 15915)	• SmPC section 4.3 *"Contraindication"* • SmPC section 4.6 *"Fertility, pregnancy and breast feeding"*
Important missing information		
Patients undergoing major orthopaedic surgery other than elective hip or knee replacement surgery	• Routine pharmacovigilance activities • Drug utilisation database studies	• SmPC (10 mg) section 4.1 *"Therapeutic indications"* and section 4.4 *"Special warnings and precautions for use"*
Patients with severe renal impairment (CrCl < 30 mL/min)	• Routine pharmacovigilance activities • Post-marketing non-interventional cohort studies (XA0801; XAMOS study 13802, XA1101; study 15914 and XA1102; study 15915)	• SmPC section 4.2 *"Posology and method of administration" (Renal impairment)* and section 4.4 *"Special warnings and precautions for use" (Renal impairment)*
Remedial pro-coagulant therapy for excessive haemorrhage	• Routine pharmacovigilance activities • Additional information from ongoing trials • Post-marketing non interventional cohort studies (XA0801; XAMOS study 13802, XA1101; study 15914 and XA1102; study 15915)	• SmPC section 4.9 *"Overdose"*
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 • Modified Prescription event monitoring study • Drug utilisation database studies • Post-marketing non-interventional cohort studies (XA0801; XAMOS study 13802, XA1101; study 15914 and XA1102; study 15915)	• SmPC section 4.5 *"Interaction with other medicinal products and other forms of interaction"*
Pregnant or breast-feeding women	• Routine pharmacovigilance activities • Drug utilisation database studies • Modified Prescription event monitoring study • Post-marketing non-interventional cohort studies (XA1101; study 15914 and XA1102; study 15915)	• SmPC section 4.3 *"Contraindication"* • SmPC section 4.6 *"Fertility, pregnancy and breast feeding"*
Patients with AF and a prosthetic heart valve	• Routine pharmacovigilance activities	• SmPC (15mg/20mg) section 4.4 *"Special warnings and precautions for use"* (*Patients with prosthetic valves)*
Long term therapy with rivaroxaban for	• Routine pharmacovigilance activities • Modified Prescription event	• All safety concerns mentioned in this chapter which may occur during long term therapy in a real life setting for VTE treatment and SPAF

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
VTE treatment and SPAF indications in real-life setting	monitoring study • Drug utilisation database studies • Post-marketing non-interventional cohort studies (XA1101; study 15914 and XA1102; study 15915)	indications are addressed in the SmPC in the relevant sections

The CHMP, having considered the data submitted in the MA application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product:

- In addition to the product information; a Patient alert card and a Prescriber guide are included as risk minimisation activities, for the VTE treatment and SPAF indications.

ORPHAN MEDICINAL PRODUCTS

N/A

User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Xarelto 10mg. The bridging report submitted by the applicant has been found acceptable.

2.8. Benefit-Risk Balance

Benefits

Acute venous thromboembolism (VTE), i.e. deep-vein thrombosis (DVT) or pulmonary embolism (PE), is a common disorder with an annual incidence rate of approximately 1-2 per thousand inhabitants. VTE is a burden for healthcare systems as it is associated with high mortality and considerable morbidity in terms of recurrent VTE, the post-thrombotic syndrome, and chronic thromboembolic pulmonary hypertension. Treatment of DVT and PE aims at prevention of extension of the existing thrombus, as well as prevention of recurrent VTE.

Standard treatment since many years for acute VTE consists of initial parenteral therapy, including low molecular weight heparin (LMWH), unfractionated heparin (UFH) or fondaparinux, overlapping with a vitamin K antagonist (VKA). Therapy with VKAs is challenged by the need for ongoing coagulation laboratory monitoring as well as by drug and food interactions. A solution to some of these issues could come from an oral anticoagulant with predictable anticoagulant activity that does not require frequent coagulation monitoring, yet effective as a single agent for acute treatment of VTE as well as the continued prevention of recurrent VTE.

This application is supported by one pivotal open-label non-inferiority study, (study11702) which has been well designed and well performed. The study population is considered sufficiently representative of the European target DVT population with regard to demographic characteristics, concomitant diseases and VTE risk factors. The composite primary and prioritised secondary endpoints are appropriate and in line with the CHMP recommendations. Measures were undertaken to reduce the potential for bias, all predefined efficacy and safety end-points were adjudicated centrally and the patients were followed on regular intervals with instructions to the investigators to evaluate key symptoms of possible outcome events. Also the patients were informed on such symptoms in a

standardised way. Treatment with rivaroxaban when compared with a well-established regimen of enoxaparin and VKA was convincingly demonstrated to be non-inferior with a hazard ratio of 0.680 (95% CI: 0.443-1.042). The test for superiority of rivaroxaban was however not statistically significant (p = 0.0764). The results were consistent in per protocol analyses and the secondary efficacy end-points supported the primary outcome. The results were consistent in important subgroups such as different age, gender, risk factors etc.

The supportive study (study 11899) which compared rivaroxaban with placebo in secondary VTE prevention that had had either rivaroxaban or VKA and had finalised the pre-planned treatment was designed as a double blind study. It provides convincing evidence of the efficacy of rivaroxaban in the secondary prevention after an acute DVT. The same composite efficacy end-point as in the pivotal study was used. Superior efficacy of rivaroxaban therapy over placebo was demonstrated with a hazard ratio of 0.185 (95% CI 0.087-0.393, p < 0.0001) or a 81% relative risk reduction. The results of the secondary end-points were supportive.

Uncertainty in the knowledge about the beneficial effects

The optimal duration of therapy has been discussed during the assessment. It was agreed by the CHMP that decisions on treatment duration should be based on the accumulated experience from treatment with VKA agents together with an assessment of the expected benefit in the individual patient taking the estimated bleeding risk into account.

It was discussed if the initial treatment with parenteral anticoagulants that the majority of patients received prior to randomisation could have contributed to the efficacy seen in the rivaroxaban group. It is, however, agreed that there is little in the compiled data that supports a general recommendation for the use of parenteral anticoagulants in the initial phase of acute treatment. The similar time of onset after administration of the two anticoagulants is supportive of this conclusion.

The efficacy results were essentially consistent in subgroups at centers with different time in therapeutic range (TTR). However, in centers with highest TTR (>70%) the observed overall tendency for better efficacy with rivaroxaban was lost. However, the CHMP believed that firm conclusions from such subgroup analyses cannot be drawn.

The size of the effect in the placebo-controlled supportive study is heavily dependent on the VTE risk in the included patients. A substantial proportion of the included patients would probably have been considered for prolonged VKA treatment in clinical routine. It appears, however, not plausible that VKA treatment would have provided much further benefit.

If approved for the proposed indication many patients will receive rivaroxaban treatment for many years and several decades. However from an efficacy perspective the provided data for long-term treatment is judged to be sufficient.

Risks

Unfavourable effects

The most important observed adverse reactions are bleedings. Reported major bleedings were not more common among the rivaroxaban treated patients as compared with the enoxaparin/VKA treated. The bleeding pattern seems to differ from what is seen during VKA treatment with a higher incidence of mucosal bleedings. The bleeding pattern has been discussed by the Applicant who claims that there are similarities in the bleeding pattern with what can be seen in inherited fX deficiency. It appears, however, reassuring that major or critical bleedings was not more common than with VKA treatment in the overall clinical study programme.

Bleeding rates in patients with moderate renal impairment tended to be increased and this may partly be related to a higher exposure of rivaroxaban in this group. A reduced dose is recommended in these patients.

There are no indications from the studies in the proposed new indication that treatment with rivaroxaban would be associated with severe hepatic adverse events. At present, there are no indications that rivaroxaban would induce thrombocytopenia or pancreatic adverse reactions.

With the exception of a possibly somewhat dissimilar bleeding pattern with a tendency for more mucosal bleedings in the rivaroxaban in the pivotal study as compared with the VKA treated group, it seems that the safety profile can be considered to be essentially similar for rivaroxaban and VKA treatment.

Uncertainty in the knowledge about the unfavourable effects

With the study design in the pivotal study, occult GI bleedings were not systematically screened for. As anaemia was somewhat more common in the rivaroxaban group appropriate recommendations for clinical and laboratory monitoring were included in the product information.

The preliminary top-line results of the large "Magellan trial" for prevention of VTE in patients with an acute medical illness has recently been submitted and show according to the preliminary study results a disturbingly high bleeding incidence in the rivaroxaban arm. As the population is at least partly overlapping with the target population for the now proposed indication the Applicant was requested to discuss the implications of the results for the current application. However, if the imbalance in bleeding observed in the heterogenous population in the "Magellan trial" would reflect a true difference in bleeding tendency similar imbalances would have been expected in the large studies in other applications. Thus the differences seen in the "Magellan trial" may at least partially have been a chance finding.

Limited experience from long-term treatment with rivaroxaban over one year is available and the overall safety database is still limited. Many of the patients treated for secondary prophylaxis of VTE can be expected to be treated for many years so a well designed risk management plan covering bleeding risks and also unexpected adverse events during prolonged treatment was approved by the CHMP.

Balance

Importance of favourable and unfavourable effects

The only available major alternative for oral long term secondary prophylaxis after DVT today is VKA treatment from which experience exists since several decades. VKA treatment requires continuous monitoring and careful consideration of numerous possibilities for interaction with other drugs and food. The quality of VKA treatment is varying between centers and patients where lower quality is associated with increased risks for bleeding and VTE recurrences. A simpler and more predictable alternative for oral use that would not need such intense monitoring would therefore be a potentially valuable alternative, especially for patients where VKA treatment is not functioning well.

VKA therapy, if well performed, is very effective in preventing recurrences after an acute DVT. From a pragmatic point of view recurrences hardly occur if INR values are kept within the therapeutic range unless there is an underlying malignancy. This application is primarily supported by an open label comparative non-inferiority study which has been well designed and performed. It has been convincingly demonstrated that rivaroxaban is not inferior to the traditional combination of parenteral anticoagulants followed by VKA treatment. The tendency for more frequent mucosal bleedings is of some concern that, however, that is judged to be manageable with adequate clinical monitoring. That

major bleedings or bleedings at critical sites were not higher among the rivaroxaban treated patients is also reassuring.

An available oral alternative to LMWH, heparin or fondaparinux injections in the acute phase could also be advantageous in some situations if carefully managed, e.g. allowing earlier discharge from hospital even if it could be argued that compliance to treatment may be higher if the drug is administered by health care professionals in this critical phase.

The overall safety profile is probably comparable with that of VKA treatment. However the limited long term safety data should be further reviewed and assessed in the ongoing clinical studies together with post marketing experience data.

2.8.1. Discussion on the benefit-risk balance

The value of an alternative with reduced need for monitoring, simpler dosing and reduced interaction potential than currently required for VKA treatment is considered to outweigh the perceived potential risks with rivaroxaban treatment.

2.8.2. Risk management plan

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.

- the following additional risk minimisation activities were required:

- A Patient alert card and a Prescriber guide are included for the VTE treatment indication.

2.9. Conclusions

The overall benefit risk of rivaroxaban in the treatment of DVT and PE is considered positive.

2.10. 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 treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults was favourable and therefore recommended the granting of the extension of marketing authorisation subject to the following conditions

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

Risk Management System

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance presented in Module 1.8.1 of the Marketing Authorisation, is in place and functioning before and whilst the medicinal product is on the market.

Risk Management Plan (RMP)

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in the RMP presented in Module 1.8.2 of the Marketing Authorisation and any subsequent updates of the RMP agreed by the Committee for Medicinal Products for Human Use (CHMP).

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency.

PSUR

The PSUR cycle for the medicinal product should follow a half-yearly cycle until otherwise agreed by the CHMP.

- ***Conditions or restrictions with regard to the safe and effective use of the medicinal product***

The MAH shall provide an educational pack, targeting all physicians who are expected to prescribe/use Xarelto, prior to the launch of the new indication for the treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT and pulmonary embolism (PE) following an acute DVT in adults.

This educational pack is aimed at increasing awareness about the potential risk of bleeding during treatment with Xarelto and providing guidance on how to manage that risk.

The MAH must agree the content and format of the educational material, together with a communication plan, with each national competent authority in the Member States prior to distribution of the educational pack in their territory.

The physician educational pack should contain:

- The Summary of Product Characteristics
- Prescriber Guide
- Patient Alert Cards

The Prescriber Guide should contain the following key safety messages:

- Details of populations potentially at higher risk of bleeding
- Recommendations for dose reduction in at risk populations
- Guidance regarding switching from or to rivaroxaban treatment
- The need for intake of the 15 mg and 20 mg tablets with food
- Management of overdose situations
- The use of coagulation tests and their interpretation
- That all patients should be provided with a Patient alert card and be
    - Signs or symptoms of bleeding and when to seek attention from a health care provider.
    - Importance of treatment compliance

- The need for intake of the 15 mg and 20 mg tablets with food
- Necessity to carry the Patient alert card with them at all times
- The need to inform Health Care Professionals that they are taking Xarelto if they need to have any surgery or invasive procedure.

The Patient alert card should contain the following key safety messages:

- Signs or symptoms of bleeding and when to seek attention from a health care provider.
- Importance of treatment compliance
- The need for intake of the 15 mg and 20 mg tablets with food
- Necessity to carry the Patient alert card with them at all times
- The need to inform Health Care Professionals that they are taking Xarelto if they need to have any surgery or invasive procedure.