PACKAGE INSERT

XABAREM 15 MG FILM-COATED TABLETS
XABAREM 20 MG FILM-COATED TABLETS

PRODUCT NAME

Xabarem 15 mg film-coated tablets
Xabarem 20 mg film-coated tablets

NAME AND STRENGTH OF ACTIVE SUBSTANCE

Xabarem 15 mg film-coated tablets: Each film-coated tablet contains 15 mg rivaroxaban.
Xabarem 20 mg film-coated tablets: Each film-coated tablet contains 20 mg rivaroxaban.

Excipient with known effect
Xabarem 15 mg film-coated tablets: Each film-coated tablet contains 16.50 mg lactose (as monohydrate).
Xabarem 20 mg film-coated tablets: Each film-coated tablet contains 22.00 mg lactose (as monohydrate).

For a full list of excipients, see section 'List of excipients'.

PRODUCT DESCRIPTION

Film-coated tablet.

Xabarem 15 mg film-coated tablets: red, round film-coated tablet debossed with '15' on one side and plain on the other side, with diameter 6.1 mm ± 5%.

Xabarem 20 mg film-coated tablets: brown-red, round film-coated tablets, debossed with "20" on one side and plain on the other side, with diameter 6.1 mm ± 5%.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Direct factor Xa inhibitors
ATC code: B01AF01

Mechanism of Action
Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of Factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated

Factor II) and no effects on platelets have been demonstrated.

Pharmacodynamic effects
Dose-dependent inhibition of Factor Xa activity was observed in humans. Prothrombin time (PT) is influenced by rivaroxaban in a dose dependent way with a close correlation to plasma concentrations (r value equals 0.98) if Neoplastin is used for the assay. Other reagents would provide different results. The readout for PT is to be done in seconds, because the INR (International Normalized Ratio) is only calibrated and validated for coumarins and cannot be used for any other anticoagulant.

In a clinical pharmacology study on the reversal of rivaroxaban pharmacodynamics in healthy adult subjects (n=22), the effects of single doses (50 IU/kg) of two different types of PCCs, a 3- factor PCC (Factors II, IX and X) and a 4-factor PCC (Factors II, VII, IX and X) were assessed. The 3-factor PCC reduced mean Neoplastin® PT values by approximately 1.0 second within 30 minutes, compared to reductions of approximately 3.5 seconds observed with the 4-factor PCC. In contrast, the 3-factor PCC had a greater and more rapid overall effect on reversing changes in endogenous thrombin generation than the 4-factor PCC *(see section 'Overdose').*

In patients receiving rivaroxaban for treatment of DVT and PE and prevention of recurrence, the 5/95 percentiles for PT (Neoplastin) 2 - 4 hours after tablet intake (i.e. at the time of maximum effect) ranged from 17 to 32 s for 15 mg rivaroxaban twice daily and from 15 to 30 s for 20 mg rivaroxaban once daily. At trough (8 - 16 h after tablet intake) the 5/95 percentiles for 15 mg twice daily ranged from 14 to 24 s and for 20 mg once daily (18- 30 h after tablet intake) from 13 to 20 s.

In patients with non-valvular atrial fibrillation receiving rivaroxaban for the prevention of stroke and systemic embolism, the 5/95 percentiles for PT (Neoplastin) 1 - 4 hours after tablet intake (i.e. at the time of maximum effect) ranged from 14 to 40 s in patients treated with 20 mg once daily and from 10 to 50 s in patients with moderate renal impairment treated with 15 mg once daily. At trough (16- 36 h after tablet intake) the 5/95 percentiles in patients treated with 20 mg once daily ranged from 12 to 26 s and in patients with moderate renal impairment treated with 15 mg once daily from 12 to 26 s.

The activated partial thromboplastin time (aPTT) and HepTest are also prolonged dose-dependently; however, they are not recommended to assess the pharmacodynamic effect of rivaroxaban. There is no need for monitoring of coagulation parameters during routine clinical treatment with rivaroxaban in clinical routine. However, if clinically indicated, rivaroxaban concentrations can be measured by calibrated quantitative anti-Factor Xa tests *(see section 'Pharmacokinetic properties').*

Paediatric population
PT (neoplastin reagent), aPTT, and anti-Xa assay (with a calibrated quantitative test) display a close correlation to plasma concentrations in children. The correlation between anti-Xa to plasma concentrations is linear with a slope close to 1. Individual discrepancies with higher or lower anti-Xa values as compared to the corresponding plasma concentrations may occur. There is no need for routine monitoring of coagulation parameters during clinical treatment with rivaroxaban. However, if clinically indicated, rivaroxaban concentrations can be measured by calibrated quantitative anti-Factor Xa tests in mcg/L. The lower limit of quantifications must be considered when the anti-Xa test is used to quantify plasma concentrations of rivaroxaban in children. No threshold for efficacy or safety events has been established.

Clinical efficacy and safety

Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation

The evidence for the efficacy and safety of rivaroxaban was derived from ROCKET AF, a multinational, double-blind study comparing rivaroxaban (at a dose of 20 mg once daily with the evening meal in patients with CrCl >50 mL/min and 15 mg once daily with the evening meal in patients with CrCl 30 to <50 mL/min) to warfarin (titrated to INR 2.0 to 3.0) to reduce the risk of stroke and non-central nervous system (CNS) systemic embolism in patients with nonvalvular atrial fibrillation (AF). Patients had to have one or more of the following additional risk factors for stroke:

- a prior stroke (ischemic or unknown type), transient ischemic attack (TIA) or non-CNS systemic embolism, or
- 2 or more of the following risk factors:
  - age ≥75 years,
  - hypertension,
  - heart failure or left ventricular ejection fraction ≤35%, or
  - diabetes mellitus

ROCKET AF was a non-inferiority study designed to demonstrate that rivaroxaban preserved more than 50% of warfarin's effect on stroke and non-CNS systemic embolism as established by previous placebo-controlled studies of warfarin in atrial fibrillation.

A total of 14264 patients were randomized and followed on study treatment for a median of 590 days. The mean age was 71 years and the mean CHADS2 score was 3.5. The population was 60% male, 83% Caucasian, 13% Asian and 1.3% Black. There was a history of stroke, TIA, or non-CNS systemic embolism in 55% of patients, and 38% of patients had not taken a vitamin K antagonist (VKA) within 6 weeks at time of screening. Concomitant diseases of patients in this study included hypertension 91%, diabetes 40%, congestive heart failure 63%, and prior myocardial infarction 17%. At baseline, 37% of patients were on aspirin (almost exclusively at a dose of 100 mg or less) and few patients were on clopidogrel. Patients were enrolled in Eastern Europe (39%); North America (19%); Asia, Australia, and New Zealand (15%); Western Europe (15%); and Latin America (13%). Patients randomized to warfarin had a mean percentage of time in the INR target range of 2.0 to 3.0 of 55%, lower during the first few months of the study.

In ROCKET AF, Rivaroxaban was demonstrated non-inferior to warfarin for the primary composite endpoint of time to first occurrence of stroke (any type) or non-CNS systemic embolism [HR (95% CI): 0.88 (0.74, 1.03)] but superiority to warfarin was not demonstrated. There are limited data on the relative effectiveness of rivaroxaban and warfarin in reducing the risk of stroke and systemic embolism when warfarin therapy is well-controlled.

Table 1 displays the overall results for the primary composite endpoint and its components.

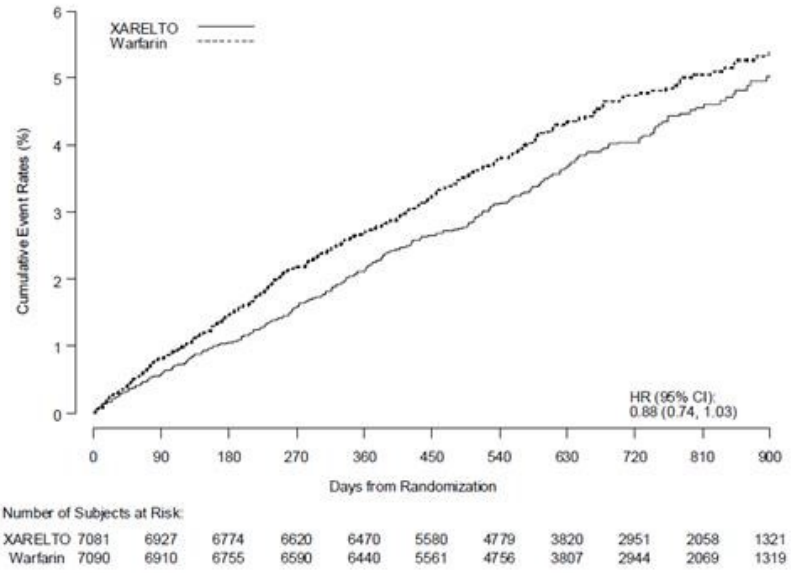
Table 1: Primary Composite Endpoint Results in ROCKET AF Study

Rivaroxaban			Warfarin		Rivaroxaban vs.Warfarin
Event	**N=7081 n (%)**	**Event Rate (per 100 Pt-yrs)**	**N=7090 n (%)**	**Event Rate (per 100 Pt-yrs)**	**Hazard Ratio (95% CI)**
Primary Composite Enpoint*	269 (3.8)	2.1	306 (4.3)	2.4	0.88 (0.74,1.03)
Stroke	253. (3.6)	2.0	281 (4.0)	2.2	
Haemorrhagic Stroke	33 (0.5)	0.3	57 (0.8)	0.4	
Ischemic Stroke	206 (2.9)	1.6	208 (2.9)	1.6	
Unknown Stroke Type	19 (0.3)	0.2	18 (0.3)	0.1	
Non-CNS Systemic Embolism	20 (0.3)	0.2	27 (0.4)	0.2	

*The primary endpoint was the time to first occurrence of stroke (any type) or non-CNS systemic embolism. Data are shown for all randomized patients followed to site notification that the study would end.

Figure 1 is a plot of the time from randomization to the occurrence of the first primary endpoint event in the two treatment arms.

Figure 1: Time to First Occurrence of Stroke (any type) or Non-CNS Systemic Embolism by Treatment Group



The efficacy of rivaroxaban was generally consistent across major subgroups.

The protocol for ROCKET AF did not stipulate anticoagulation after study drug discontinuation, but warfarin patients who completed the study were generally maintained on warfarin. Rivaroxaban patients were generally switched to warfarin without a period of co-administration of warfarin and Rivaroxaban, so that they were not adequately anticoagulated after stopping Rivaroxaban until attaining a therapeutic INR. During the 28 days following the end of the study, there were 22 strokes in the 4637 patients taking Rivaroxaban vs. 6 in the 4691 patients taking warfarin.

Few patients in ROCKET AF underwent electrical cardioversion for atrial fibrillation. The utility of Rivaroxaban for preventing post-cardioversion stroke and systemic embolism is unknown.

In addition to the phase III ROCKET AF study, a prospective, single-arm, post-authorization, non-interventional, open-label cohort study (XANTUS) with central outcome adjudication including thromoboembolic events and major bleeding has been conducted. 6,785 patients with non-valvular atrial fibrillation were enrolled for prevention of stroke and non-central nervous system (CNS) systemic embolism under real-world conditions. The mean CHADS2 score was 2.0 compared to a mean CHADS2 score of 3.5 in ROCKET AF. Major bleeding occurred in 2.1 per 100 patient years. Fatal haemorrhage was reported in 0.2 per 100 patient years and intracranial haemorrhage in 0.4 per 100 patient years. Stroke or non-CNS systemic embolism was recorded in 0.8 per 100 patient years. These observations from routine clinical practice are consistent with the results observed in the ROCKET AF study.

Prevention of cardiovascular events in non-valvular atrial fibrillation patients scheduled for cardioversion

A prospective, randomized, open-label, multicenter, exploratory study with blinded endpoint evaluation (X-VERT) was conducted in 1504 patients (oral anticoagulant naïve and pre-treated) with non-valvular atrial fibrillation scheduled for cardioversion to compare rivaroxaban with dose-adjusted VKA (randomized 2:1), for the prevention of cardiovascular events. TEE- guided (1-5 days of pre-treatment) or conventional cardioversion (at least three weeks of pre-treatment) strategies were employed. The primary efficacy outcome (all stroke, transient ischemic attack, non-CNS systemic embolism, MI and cardiovascular death) occurred in 5 (0.5%) patients in the rivaroxaban group (n=978) and 5 (1.0%) patients in the VKA group (n=492; RR 0.50; 95% CI 0.15-1.73; modified ITT population). The principal safety outcome (major bleeding) occurred in 6 (0.6%) and 4 (0.8%) patients in the rivaroxaban (n=988) and VKA (n=499) groups, respectively (RR 0.75; 95% CI 0.21-2.66; safety population). This exploratory study showed comparable efficacy and safety between rivaroxaban and VKAs treatment groups in the setting of cardioversion.

SPAF: Patients who undergo PCI with stent placement

A randomized, open-label, multicenter study (PIONEER AF-PCI) was conducted in 2124 patients with non-valvular atrial fibrillation who underwent PCI with stent placement for primary atherosclerotic disease to compare safety of two rivaroxaban regimens and one VKA regimen. Patients were randomly assigned in a 1:1:1 fashion for an overall 12 month-therapy. Patients with a history of stroke or TIA were excluded.

Group 1 received rivaroxaban 15 mg once daily (10 mg once daily in patients with CrCl: 30 to <50 mL/min) plus P2Y12 inhibitor. Group 2 received rivaroxaban 2.5 mg twice daily plus DAPT (dual antiplatelet therapy i.e. clopidogrel 75 mg [or alternate P2Y12 inhibitor] plus low-dose acetylsalicylic acid [ASA]) for 1, 6 or 12 months followed by rivaroxaban 15 mg (or 10 mg for subjects with CrCl: 30 to <50 mL/min) once daily plus low-dose ASA. Group 3 received dose- adjusted VKA plus DAPT for 1, 6 or 12 months followed by dose-adjusted VKA plus low-dose ASA. Majority of the patients received clopidogrel for the P2Y12 inhibitor.

The primary safety endpoint, clinically significant bleeding events, occurred in 109 (15.7%), 117 (16.6%), and 167 (24.0%) subjects in group 1, group 2, and group 3, respectively (HR 0.59; 95% CI 0.47-0.76; p<0.001 for group 1 vs. group 3, and HR 0.63; 95% CI 0.50-0.80; p<0.001, for group 2 vs. group 3, respectively). Each of the rivaroxaban regimens showed a significant reduction in clinically significant bleeding events compared to the VKA regimen in patients with non-valvular atrial fibrillation who underwent a PCI with stent placement. The secondary endpoint (composite of cardiovascular events including CV death, MI, or stroke) occurred in 41 (5.9%), 36(5.1%), and 36 (5.2%) subjects in the group 1, group 2, and group 3 respectively. (HR 1.08; 95%CI 0.69-1.68; p=0.750 for group 1 vs. group 3, and HR 0.93; 95% CI 0.59-1.48; p=0.765 for group 2 vs. group 3; respectively. The study was not designed to compare efficacy between the treatment arms.
The primary objective of PIONEER AF-PCI was to assess safety. Data of efficacy (including thromboembolic events) in this population are limited.

Treatment of DVT, PE and prevention of recurrent DVT and PE
The rivaroxaban clinical program was designed to demonstrate the efficacy of rivaroxaban in the initial and continued treatment of acute DVT, PE and prevention of recurrence.
Over 12800 patients were studied in four randomized controlled phase III clinical studies (Einstein DVT, Einstein PE, Einstein Extension and EINSTEIN CHOICE) and additionally a predefined pooled analysis of the Einstein DVT and Einstein PE studies was conducted. The overall combined treatment duration in all studies was up to 21 months.
In Einstein DVT 3,449 patients with acute DVT were studied for the treatment of DVT and the prevention of recurrent DVT and PE (patients who presented with symptomatic PE were excluded from this study). The treatment duration was for 3, 6 or 12 months depending on the clinical judgement of the investigator.

For the initial 3 week treatment of acute DVT 15 mg rivaroxaban was administered twice daily. This was followed by 20 mg rivaroxaban once daily.

In Einstein PE, 4,832 patients with acute PE were studied for the treatment of PE and the prevention of recurrent DVT and PE. The treatment duration was for 3, 6 or 12 months depending on the clinical judgement of the investigator.

For the initial treatment of acute PE 15 mg rivaroxaban was administered twice daily for three weeks. This was followed by 20 mg rivaroxaban once daily.

In both the Einstein DVT and the Einstein PE study, the comparator treatment regimen consisted of enoxaparin administered for at least 5 days in combination with vitamin K antagonist treatment until the PT/INR was in therapeutic range (≥2.0). Treatment was continued with a vitamin K antagonist dose-adjusted to maintain the PT/INR values within the therapeutic range of 2.0 to 3.0.

In Einstein Extension 1,197 patients with DVT or PE were studied for the prevention of recurrent DVT and PE. The treatment duration was for an additional 6 or 12 months in patients who had completed 6 to 12 months of treatment for venous thromboembolism depending on the clinical judgment of the investigator. Rivaroxaban 20 mg once daily was compared with placebo.

EINSTEIN DVT, PE and Extension used the same pre-defined primary and secondary efficacy outcomes. The primary efficacy outcome was symptomatic recurrent VTE defined as the composite of recurrent DVT or fatal or non-fatal PE. The secondary efficacy outcome was defined as the composite of recurrent DVT, non-fatal PE and all cause mortality.

In EINSTEIN CHOICE, 3,396 patients with confirmed symptomatic DVT and/or PE who completed 6-12 months of anticoagulant treatment were studied for the prevention of fatal PE or non-fatal symptomatic recurrent DVT or PE. Patients with an indication for continued therapeutic-dosed anticoagulation were excluded from the study. The treatment duration was up to 12 months depending on the individual randomization date (median: 351 days). rivaroxaban 20 mg once daily and rivaroxaban 10 mg once daily were compared with 100 mg acetylsalicylic acid once daily.

The primary efficacy outcome was symptomatic recurrent VTE defined as the composite of recurrent DVT or fatal or non-fatal PE. The secondary efficacy outcome was the composite of the primary efficacy outcome, MI, ischemic stroke, or non-CNS systemic embolism.

In the Einstein DVT study (see Table 1) rivaroxaban was demonstrated to be non-inferior to enoxaparin/VKA for the primary efficacy outcome ($p < 0.0001$ (test for non-inferiority); hazard ratio: 0.680 (0.443 - 1.042), p=0.076 (test for superiority). The prespecified net clinical benefit (primary efficacy outcome plus major bleeding events) was reported with a hazard ratio of 0.67 (95% CI: = 0.47–0.95), nominal p value p=0.027) in favour of rivaroxaban. INR values were within the therapeutic range a mean of 60.3% of the time for the mean treatment duration of 189 days, and 55.4%, 60.1%, and 62.8% of the time in the 3- , 6- , and 12- month intended treatment duration groups, respectively. In the enoxaparin/VKA group, there was no clear relation between the level of mean centre TTR (Time in Target INR Range of 2.0 – 3.0) in the equally sized tertiles and the incidence of the recurrent VTE (P=0.932 for interaction). Within the highest tertile according to centre, the hazard ratio with rivaroxaban versus warfarin was 0.69 (95% CI: 0.35- 1.35).

The incidence rates for the primary safety outcome (major or clinically relevant non-major bleeding events) as well as the secondary safety outcome (major bleeding events) were similar for both treatment groups.

Table 2: Efficacy and safety results from phase III Einstein DVT

Study population	**3,449 patients with symptomatic acute deep vein thrombosis**	
Treatment dosage and duration	Rivaroxaban [a] 3, 6 or 12 months N=1,731	Enoxaparin/VKA[b] 3, 6 or 12 months N=1,718
Symptomatic recurrent VTE*	36 (2.1%)	51 (3.0%)
Symptomatic recurrent PE	20 (1.2%)	18 (1.0%)

Symptomatic recurrent DVT	14 (0.8%)	28 (1.6%)
Symptomatic PE and DVT	1 (0.1%)	0
Fatal PE/Death where PE cannot be ruled out	4 (0.2%)	6 (0.3%)
Major or clinically relevant non-major bleeding	139 (8.1%)	138 (8.1%)
Major bleeding events	14 (0.8%)	20 (1.2%)

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily
b) Enoxaparin for at least 5 days, overlapped with and followed by VKA
* $p < 0.0001$ (non-inferiority to a prespecified hazard ratio of 2.0); hazard ratio: 0.680 (0.443 1.042), p=0.076 (superiority)

In the Einstein PE study (see Table 3) rivaroxaban was demonstrated to be non-inferior to enoxaparin/VKA for the primary efficacy outcome (p=0.0026 (test for non-inferiority); hazard ratio: 1.123 (0.749 – 1.684)). The prespecified net clinical benefit (primary efficacy outcome plus major bleeding events) was reported with a hazard ratio of 0.849 ((95% CI: 0.633 - 1.139), nominal p value p= 0.275). INR values were within the therapeutic range a mean of 63% of the time for the mean treatment duration of 215 days, and 57%, 62%, and 65% of the time in the 3-, 6-, and 12-month intended treatment duration groups, respectively. In the enoxaparin/VKA group, there was no clear relation between the level of mean centre TTR (Time in Target INR Range of 2.0 – 3.0) in the equally sized tertiles and the incidence of the recurrent VTE (p=0.082 for interaction). Within the highest tertile according to centre, the hazard ratio with rivaroxaban versus warfarin was 0.642 (95% CI: 0.277 - 1.484).

The incidence rates for the primary safety outcome (major or clinically relevant non-major bleeding events) was slightly lower in the rivaroxaban treatment group (10.3% (249/2412)) than in the enoxaparin/VKA treatment group (11.4% (274/2405)). The incidence of the secondary safety outcome (major bleeding events) was lower in the rivaroxaban group (1.1% (26/2412)) than in the enoxaparin/VKA group (2.2% (52/2405)) with a hazard ratio 0.493 (95% CI: 0.308 - 0.789).

Table 3: Efficacy and safety results from phase III Einstein PE

Study population	**4,832 patients with an acute symptomatic PE**	
Treatment dosage and duration	Rivaroxaban [a] 3, 6 or 12 months N=2,419	Enoxaparin/VKA [b] 3, 6 or 12 months N=2,413
Symptomatic recurrent VTE*	50 (2.1%)	44 (1.8%)
Symptomatic recurrent PE	23 (1.0%)	20 (0.8%)
Symptomatic recurrent DVT	18 (0.7%)	17 (0.7%)
Symptomatic PE and DVT	0	2 (<0.1%)
Fatal PE/Death where PE cannot be ruled out	11 (0.5%)	7 (0.3%)

Major or clinically relevant non-major bleeding	249 (10.3%)	274 (11.4%)
Major bleeding events	26 (1.1%)	52 (2.2%)

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily
b) Enoxaparin for at least 5 days, overlapped with and followed by VKA
* $p < 0.0026$ (non-inferiority to a prespecified hazard ratio of 2.0); hazard ratio: 1.123 (0.749 - 1.684)

A prespecified pooled analysis of the outcome of the Einstein DVT and PE studies was conducted (see Table 4).

Table 4: Efficacy and safety results from pooled analysis of phase III Einstein DVT and Einstein PE

Study population	**8,281 patients with an acute symptomatic DVT or PE**	
Treatment dosage and duration	Rivaroxaban [a] 3, 6 or 12 months N=4,150	Enoxaparin/VKA[b] 3, 6 or 12 months N=4,131
Symptomatic recurrent VTE*	86 (2.1%)	95 (2.3%)
Symptomatic recurrent PE	43 (1.0%)	38 (0.9%)
Symptomatic recurrent DVT	32 (0.8%)	45 (1.1%)
Symptomatic PE and DVT	1 (<0.1%)	2 (<0.1%)
Fatal PE/Death where PE cannot be ruled out	15 (0.4%)	13 (0.3%)
Major or clinically relevant non-major bleeding	388 (9.4%)	412 (10.0%)
Major bleeding events	40 (1.0%)	72 (1.7%)

a) Rivaroxaban 15 mg twice daily for 3 weeks followed by 20 mg once daily
b) Enoxaparin for at least 5 days, overlapped with and followed by VKA
* $p < 0.0001$ (non-inferiority to a prespecified hazard ratio of 1.75); hazard ratio: 0.886 (0.661 – 1.186)

The prespecified net clinical benefit (primary efficacy outcome plus major bleeding events) of the pooled analysis was reported with a hazard ratio of 0.771 ((95% CI: 0.614 – 0.967), nominal p value p = 0.0244).

In the Einstein Extension study (see Table 5) rivaroxaban was superior to placebo for the primary and secondary efficacy outcomes. For the primary safety outcome (major bleeding events) there was a non-significant numerically higher incidence rate for patients treated with rivaroxaban 20 mg once daily compared to placebo. The secondary safety outcome (major or clinically relevant non-major bleeding events) showed higher rates for patients treated with rivaroxaban 20 mg once daily compared to placebo.

Table 5: Efficacy and safety results from phase III Einstein Extension

Study population	**1,197 patients continued treatment and prevention of recurrent venous thromboembolism**	
Treatment dosage and duration	Rivaroxaban [a] 6 or 12 months N=602	Placebo 6 or 12 months N=594
Symptomatic recurrent VTE*	8 (1.3%)	42 (7.1%)
Symptomatic recurrent PE	2 (0.3%)	13 (2.2%)
Symptomatic recurrent DVT	5 (0.8%)	31 (5.2%)
Fatal PE/Death where PE cannot be ruled out	1 (0.2%)	1 (0.2%)
Major bleeding events	4 (0.7%)	0 (0.0%)
Clinically relevant non-major bleeding	32 (5.4%)	7 (1.2%)

a) Rivaroxaban 20 mg once daily

* $p < 0.0001$ (superiority), hazard ratio: 0.185 (0.087 - 0.393)

In the EINSTEIN CHOICE study rivaroxaban 20 mg and 10 mg were both superior to 100 mg acetylsalicylic acid for the primary efficacy outcome. The secondary efficacy outcome was significantly reduced when comparing rivaroxaban 20 mg or 10 mg vs. 100 mg acetylsalicylic acid. The principal safety outcome (major bleeding events) was similar for patients treated with rivaroxaban 20 mg and 10 mg once daily compared to 100 mg acetylsalicylic acid. The secondary safety outcome (non-major bleeding associated with treatment cessation of more than 14 days) was similar when comparing rivaroxaban 20 mg or 10 mg vs. 100 mg acetylsalicylic acid. Outcomes were consistent across the patients with provoked and unprovoked VTE (see Table 5).

In a prespecified net clinical benefit analysis (NCB) (primary efficacy outcome plus major bleeding events) of EINSTEIN CHOICE, a HR of 0.44 (95% CI 0.27 - 0.71, p=0.0009) for rivaroxaban 20 mg once daily vs 100 mg acetylsalicylic acid once daily and a HR of 0.32 (95% CI 0.18 - 0.55, p<0.0001) for rivaroxaban 10 mg once daily vs 100 mg acetylsalicylic acid once daily were reported.

Table 6: Efficacy and safety results from phase III EINSTEIN CHOICE

Study population	**3,396 patients continued prevention of recurrent venous thromboembolism**		
Treatment dosage	Rivaroxaban 20 mg od N=1,107	Rivaroxaban 10 mg od N=1,127	ASA 100 mg od N=1,131
Treatment duration, median [interquartile range]	349 [189-362] days	353 [190-362] days	350 [186-362] days
Symptomatic recurrent VTE	17 (1.5%)*	13 (1.2%)**	50 (4.4%)

Symptomatic recurrent PE	6 (0.5%)	6 (0.5%)	19 (1.7%)
Symptomatic recurrent DVT	9 (0.8%)	8 (0.7%)	30 (2.7%)
Fatal PE/death where PE cannot be ruled out	2 (0.2%)	0	2 (0.2%)
Major bleeding events	6 (0.5%)	5 (0.4%)	3 (0.3%)

*p<0.001(superiority) Rivaroxaban 20 mg od vs ASA 100 mg od; HR=0.34 (0.20–0.59)
** p<0.001 (superiority) Rivaroxaban 10 mg od vs ASA 100 mg od; HR=0.26 (0.14–0.47)

In addition to the phase III EINSTEIN program, a prospective, non-interventional, open-label cohort study (XALIA) with central outcome adjudication including recurrent VTE, major bleeding and death has been conducted. 5,142 patients with acute DVT were enrolled to investigate the long-term safety of rivaroxaban compared with standard-of-care anticoagulation therapy under real-world conditions. Rates of major bleeding, recurrent VTE and all-cause mortality for rivaroxaban were 0.7%, 1.4% and 0.5%, respectively. There were differences in patient baseline characteristics including age, cancer and renal impairment. A pre-specified propensity score stratified analyses was used to adjust for measured baseline differences but residual confounding may, in spite of this, influence the results. Adjusted hazard ratios for major bleeding, recurrent VTE and all-cause mortality were 0.77 (95% CI 0.40-1.50), 0.91 (95% CI 0.54-1.54) and 0.51 (95% CI 0.24-1.07), respectively.

Rivaroxaban showed similar safety and efficacy compared to standard anticoagulation.
These results in patients who were observed in routine clinical practice are consistent with those observed in the EINSTEIN DVT study.

Paediatric population
Treatment of VTE and prevention of VTE recurrence in paediatric patients
A total of 727 children with confirmed acute VTE, of whom 528 received rivaroxaban, were studied in 6 open-label, multicentre paediatric studies. Body weight-adjusted dosing in patients from birth to less than 18 years resulted in rivaroxaban exposure similar to that observed in adult DVT patients treated with rivaroxaban 20 mg once daily as confirmed in the phase III study *(see section 'Pharmacokinetic properties').*

The EINSTEIN Junior phase III study was a randomised, active-controlled, open-label multicentre clinical study in 500 paediatric patients (aged from birth to < 18 years) with confirmed acute VTE.

There were 276 children aged 12 to < 18 years, 101 children aged 6 to < 12 years, 69 children aged 2 to < 6 years, and 54 children aged < 2 years.

Index VTE was classified as either central venous catheter-related VTE (CVC-VTE; acute: 56.7%90/335 patients in the rivaroxaban group, 37/165 patients in the comparator group), cerebral vein and sinus thrombosis (CVST; acute: 88.0%74/335 patients in the rivaroxaban group, 43/165 patients in the comparator group), and all others including DVT and PE (non-CVC-VTE; acute: 87.1%171/335 patients in the rivaroxaban group, 84/165 patients in the comparator group). The most common presentation of index thrombosis in children aged 12 to < 18 years was non- CVC-VTE in 211 (76.4%); in children aged 6 to < 12 years and aged 2 to < 6 years was CVST in 48 (47.5%) and 35

(50.7%), respectively; and in children aged < 2 years was CVC-VTE in 37 (68.5%). There were no children < 6 months with CVST in the rivaroxaban group. 22 of the patients with CVST had a CNS infection (13 patients in the rivaroxaban group and 9 patients in comparator group).

VTE was provoked by persistent, transient, or both persistent and transient risk factors in 438 (87.6%) children.

Patients received initial treatment with therapeutic doses of UFH, LMWH, or fondaparinux for at least 5 days, and were randomised 2:1 to receive either body weight-adjusted doses of rivaroxaban or comparator group (heparins, VKA) for a main study treatment period of 3 months (1 month for children < 2 years with CVC-VTE). At the end of the main study treatment period, the diagnostic imaging test, which was obtained at baseline, was repeated, if clinically feasible. The study treatment could be stopped at this point, or at the discretion of the Investigator continued for up to 12 months (for children < 2 years with CVC-VTE up to 3 months) in total.

The primary efficacy outcome was symptomatic recurrent VTE. The primary safety outcome was the composite of major bleeding and clinically relevant non-major bleeding (CRNMB). All efficacy and safety outcomes were centrally adjudicated by an independent committee blinded for treatment allocation. The efficacy and safety results are shown in Tables 11 and 12 below.

Recurrent VTEs occurred in the rivaroxaban group in 4 of 335 patients and in the comparator group in 5 of 165 patients. The composite of major bleeding and CRNMB was reported in 10 of 329 patients (3%) treated with rivaroxaban and in 3 of 162 patients (1.9%) treated with comparator. Net clinical benefit (symptomatic recurrent VTE plus major bleeding events) was reported in the rivaroxaban group in 4 of 335 patients and in the comparator group in 7 of 165 patients. Normalisation of the thrombus burden on repeat imaging occurred in 128 of 335 patients with rivaroxaban treatment and in 43 of 165 patients in the comparator group. These findings were generally similar among age groups. There were 119 (36.2%) children with any treatment emergent bleeding in the rivaroxaban group and 45 (27.8%) children in the comparator group.

Table 7: Efficacy results at the end of the main treatment period

Event	**Rivaroxaban N=335***	**Comparator N=165***
Recurrent VTE (primary efficacy outcome)	4 (1.2%, 95% CI 0.4% – 3.0%)	5 (3.0%, 95% CI 1.2% - 6.6%)
Composite: Symptomatic recurrent VTE + asymptomatic deterioration on repeat imaging	5 (1.5%, 95% CI 0.6% – 3.4%)	6 (3.6%, 95% CI 1.6% – 7.6%)
Composite: Symptomatic recurrent VTE + asymptomatic deterioration + no change on repeat imaging	21 (6.3%, 95% CI 4.0% – 9.2%)	19 (11.5%, 95% CI 7.3% – 17.4%)
Normalisation on repeat imaging	128 (38.2%, 95% CI 33.0% - 43.5%)	43 (26.1%, 95% CI 19.8% - 33.0%)
Fatal or non-fatal pulmonary embolism	4 (1.2%, 95% CI 0.4% - 3.0%)	7 (4.2%, 95% CI 2.0% - 8.4%)

Fatal or non-fatal pulmonary embolism	1 (0.3%, 95% CI 0.0% – 1.6%)	1 (0.6%, 95% CI 0.0% – 3.1%)

*FAS= full analysis set, all children who were randomised

Table 8: Safety results at the end of the main treatment period

	Rivaroxaban N=329*	**Comparator N=162***
Composite: Major bleeding + CRNMB (primary safety outcome)	10 (3.0%, 95% CI 1.6% - 5.5%)	3 (1.9%, 95% CI 0.5% - 5.3%)
Major bleeding	0 (0.0%, 95% CI 0.0% - 1.1%)	2 (1.2%, 95% CI 0.2% - 4.3%)
Any treatment-emergent bleedings	119 (36.2%)	45 (27.8%)

*SAF = safety analysis set, all children who were randomised and received at least 1 dose of study medicinal product

The efficacy and safety profile of rivaroxaban was largely similar between the paediatric VTE population and the DVT/PE adult population, however, the proportion of subjects with any bleeding was higher in the paediatric VTE population as compared to the DVT/PE adult population.

Patients with high risk triple positive antiphospholipid syndrome
In an investigator sponsored randomized open-label multicenter study with blinded endpoint adjudication, rivaroxaban was compared to warfarin in patients with a history of thrombosis, diagnosed with antiphospholipid syndrome and at high risk for thromboembolic events (positive for all 3 antiphospholipid tests: lupus anticoagulant, anticardiolipin antibodies, and anti–beta 2- glycoprotein I antibodies). The trial was terminated prematurely after the enrollment of 120 patients due to an excess of events among patients in the rivaroxaban arm. Mean follow-up was 569 days. Fifty-nine patients were randomized to rivaroxaban 20 mg (15 mg for patients with creatinine clearance <50 mL/min) and 61 to warfarin (INR 2.0-3.0). Thromboembolic events occurred in 12% of patients randomized to rivaroxaban (4 ischaemic stroke and 3 myocardial infarction). No events were reported in patients randomized to warfarin. Major bleeding occurred in 4 patients (7%) of the rivaroxaban group and 2 patients (3%) of the warfarin group.

Pharmacokinetic properties

Absorption and Bioavailability
The following information is based on the data obtained in adults.

Rivaroxaban is rapidly absorbed with maximum concentrations (C_{max}) appearing 2-4 hours after tablet intake.

Oral absorption of rivaroxaban is almost complete and oral bioavailability is high (80 - 100%) for the 10 mg tablet dose, irrespective of fasting/fed conditions. Intake with food does not affect rivaroxaban AUC or C_{max} at the 10 mg dose.

Due to a reduced extent of absorption an oral bioavailability of 66% was determined for the 20 mg tablet under fasting conditions. When rivaroxaban 20 mg tablets are taken together with food increases in mean AUC by 39% were observed when compared to tablet intake under fasting conditions, indicating almost complete absorption and high oral bioavailability. Xabarem 15 mg and 20 mg are to be taken with food *(see section 'Dosage and method of administration').*

Under fed conditions rivaroxaban 10 mg, 15 mg and 20 mg tablets demonstrated dose-proportionality. Variability in rivaroxaban pharmacokinetics is moderate with inter-individual variability (CV%) ranging from 30% to 40%.

Absorption of rivaroxaban is dependent on the site of drug release in the GI tract. A 29% and 56% decrease in AUC and C_{max} compared to tablet was reported when rivaroxaban granulate is released in the proximal small intestine. Exposure is further reduced when drug is released in the distal small intestine, or ascending colon. Avoid administration of rivaroxaban distal to the stomach which can result in reduced absorption and related drug exposure.

In a study with 44 healthy subjects, both mean AUC and C_{max} values for 20 mg rivaroxaban administered orally as a crushed tablet mixed in applesauce were comparable to that after the whole tablet. However, for the crushed tablet suspended in water and administered via a nasogastric tube followed by a liquid meal only, only mean AUC was comparable to that after the whole tablet, and C_{max} was 18% lower. Given, the predictable, dose-proportional pharmacokinetic profile of rivaroxaban, the bioavailability results from this study are likely applicable to lower rivaroxaban doses.

Paediatric population

Children received rivaroxaban tablet or oral suspension during or closely after feeding or food intake and with a typical serving of liquid to ensure reliable dosing in children. As in adults, rivaroxaban is readily absorbed after oral administration as tablet or granules for oral suspension formulation in children. No difference in the absorption rate nor in the extent of absorption between the tablet and granules for oral suspension formulation was observed. No PK data following intravenous administration to children are available so that the absolute bioavailability of rivaroxaban in children is unknown. A decrease in the relative bioavailability for increasing doses (in mg/kg bodyweight) was found, suggesting absorption limitations for higher doses, even when taken together with food.
Rivaroxaban 15 mg and 20 mg tablets should be taken with feeding or with food *(see section 'Dosage and method of administration').*

Distribution

Plasma protein binding in adults is high at approximately 92 % to 95 %, with serum albumin being the main binding component. The volume of distribution is moderate with V_{ss} being approximately 50 litres.

Paediatric population

No data on rivaroxaban plasma protein binding specific to children is available. No PK data following intravenous administration of rivaroxaban to children is available. V_{ss} estimated via population PK modelling in children (age range 0 to < 18 years) following oral administration of rivaroxaban is dependent on body weight and can be described with an allometric function, with an average of 113 L for a subject with a body weight of 82.8 kg.

Metabolism and Elimination
In adults, of the administered rivaroxaban dose, approximately 2/3 undergoes metabolic degradation, with half then being eliminated renally and the other half eliminated by the faecal route. The final 1/3 of the administered dose undergoes direct renal excretion as unchanged active substance in the urine, mainly via active renal secretion.

Rivaroxaban is metabolised via CYP3A4, CYP2J2 and CYP-independent mechanisms. Oxidative degradation of the morpholinone moiety and hydrolysis of the amide bonds are the major sites of biotransformation. Based on *in vitro* investigations rivaroxaban is a substrate of the transporter proteins P-gp (P-glycoprotein) and Bcrp (breast cancer resistance protein).

Unchanged rivaroxaban is the most important compound in human plasma, with no major or active circulating metabolites being present. With a systemic clearance of about 10 l/h, rivaroxaban can be classified as a low-clearance drug. After intravenous administration of a 1 mg dose the elimination half-life is about 4.5 hours. After oral administration the elimination becomes absorption rate limited. Elimination of rivaroxaban from plasma occurs with terminal half-lives of 5 to 9 hours in young individuals, and with terminal half-lives of 11 to 13 hours in the elderly.

Paediatric population
No metabolism data specific to children is available. No PK data following intravenous administration of rivaroxaban to children is available. CL estimated via population PK modelling in children (age range 0 to < 18 years) following oral administration of rivaroxaban is dependent on body weight and can be described with an allometric function, with an average of 8 L/h for a subject with body weight of 82.8 kg. The geometric mean values for disposition half-lives (t1/2) estimated via population PK modelling decrease with decreasing age and ranged from 4.2 h in adolescents to approximately 3 h in children aged 2-12 years down to 1.9 and 1.6 h in children aged 0.5-< 2 years and less than 0.5 years, respectively.

Special populations
Gender
In adults, there were no clinically relevant differences in pharmacokinetics and pharmacodynamics between male and female patients.
An exploratory analysis did not reveal relevant differences in rivaroxaban exposure between male and female children

Geriatric patients
Elderly patients exhibited higher plasma concentrations than younger patients, with mean AUC values being approximately 1.5 fold higher, mainly due to reduced (apparent) total and renal clearance. No dose adjustment is necessary.

Body weight
In adults, extremes in body weight (< 50 kg or > 120 kg) had only a small influence on rivaroxaban plasma concentrations (less than 25 %). No dose adjustment is necessary.
In children, rivaroxaban is dosed based on body weight. An exploratory analysis did not reveal a relevant impact of underweight or obesity on rivaroxaban exposure in children.

Ethnic differences
Healthy Japanese subjects were found to have 20 to 40% on average, higher exposures compared to other ethinicities including Chinese. However, these differences in exposure are reduced when values are corrected for body weight.

An exploratory analysis did not reveal relevant inter-ethnic differences in rivaroxaban exposure among Japanese, Chinese or Asian children outside Japan and China compared to the respective overall paediatric population.

Hepatic impairment
Cirrhotic adult patients with mild hepatic impairment (classified as Child Pugh A) exhibited only minor changes in rivaroxaban pharmacokinetics (1.2 fold increase in rivaroxaban AUC on average), nearly comparable to their matched healthy control group. In cirrhotic patients with moderate hepatic impairment (classified as Child Pugh B), rivaroxaban mean AUC was significantly increased by 2.3 fold compared to healthy volunteers. Unbound AUC was increased 2.6 fold. These patients also had reduced renal elimination of rivaroxaban, similar to patients with moderate renal impairment. There are no data in patients with severe hepatic impairment.
The inhibition of Factor Xa activity was increased by a factor of 2.6 in patients with moderate hepatic impairment as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 2.1. Patients with moderate hepatic impairment were more sensitive to rivaroxaban resulting in a steeper PK/PD relationship between concentration and PT.
Rivaroxaban is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including cirrhotic patients with Child Pugh B and C *(see section 'Contraindications').*

No clinical data is available in children with hepatic impairment.

Renal impairment
In adults, there was an increase in rivaroxaban exposure correlated to decrease in renal function, as assessed via creatinine clearance measurements. In individuals with mild (creatinine clearance 50 - 80 ml/min), moderate (creatinine clearance 30 - 49 ml/min) and severe (creatinine clearance 15 - 29 ml/min) renal impairment, rivaroxaban plasma concentrations (AUC) were increased 1.4, 1.5 and 1.6 fold respectively. Corresponding increases in pharmacodynamic effects were more pronounced. In individuals with mild, moderate and severe renal impairment the overall inhibition of factor Xa activity was increased by a factor of 1.5, 1.9 and 2.0 respectively as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 1.3, 2.2 and 2.4 respectively. There are no data in patients with creatinine clearance < 15 ml/min.

Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

Use is not recommended in patients with creatinine clearance < 15 ml/min. Xabarem is to be used with caution in patients with creatinine clearance 15 - 29 ml/min *(see section 'Warnings and precautions').*

No clinical data is available in children 1 year or older with moderate or severe renal impairment (glomerular filtration rate < 50 mL/min/1.73 m^2).

<u>Pharmacokinetic data in patients</u>

In patients receiving rivaroxaban for treatment of acute DVT 20 mg once daily the geometric mean concentration (90% prediction interval) 2 - 4 h and about 24 h after dose (roughly representing maximum and minimum concentrations during the dose interval) was 215 (22 - 535) and 32 (6 - 239) mcg/l, respectively.

In paediatric patients with acute VTE receiving body weight-adjusted rivaroxaban leading to an exposure similar to that in adult DVT patients receiving a 20 mg once daily dose, the geometric mean concentrations (90% interval) at sampling time intervals roughly representing maximum and minimum concentrations during the dose interval are summarised in Table 9.

Table 9: Summary statistics (geometric mean (90% interval)) of rivaroxaban steady state plasma concentrations (mcg/L) by dosing regimen and age

Time **intervals**								
o.d.	**N**	**12 - < 18 years**	**N**	**6 -< 12 years**				
2.5-4h post	171	241.5 (105-484)	24	229.7 (91.5-777)				
20-24h post	151	20.6 (5.69-66.5)	24	15.9 (3.42-45.5)				
b.i.d.	**N**	**6 -< 12 years**	**N**	**2 -< 6 years**	**N**	**0.5 -< 2 years**		
2.5-4h post	36	145.4 (46.0-343)	38	171.8 (70.7-438)	2	n.c.		
10-16h post	33	26.0 (7.99-94.9)	37	22.2 (0.25-127)	3	10.7 (n.c.-n.c.)		
t.i.d.	**N**	**2 -< 6 years**	**N**	**Birth - < 2 years**	**N**	**0.5 -< 2 years**	**N**	**Birth - < 0.5 years**
0.5-3h post	5	164.7 (108-283)	25	111.2 (22.9-320)	13	114.3 (22.9-346)	12	108.0 (19.2-320)
7-8h post	3	33.2 (18.7-99.7)	23	18.7 (10.1-36.5)	12	21.4 (10.5-65.6)	11	16.1 (1.03-33.6)

o.d. = once daily, b.i.d. = twice daily, t.i.d. three times daily, n.c. = not calculated
Values below lower limit of quantification (LLOQ) were substituted by 1/2 LLOQ for the calculation of statistics (LLOQ = 0.5 mcg/L).

Pharmacokinetic/pharmacodynamic relationship

The Pharmacokinetic/pharmacodynamic (PK/PD) relationship between rivaroxaban plasma concentration and several PD endpoints (Factor Xa inhibition, PT, aPTT, Heptest) has been evaluated after administration of a wide range of doses (5 - 30 mg bid). Rivaroxaban 15 mg bid or 20 mg od results in a steady state C_{max} of about 255 – 275 µg/l. The relationship between rivaroxaban concentration and Factor Xa activity was best described by an E_{max} model. For PT, the linear intercept model generally described the data better. Depending on the different PT reagents used, the slope differed considerably. When Neoplastin PT was used, baseline PT was about 13 s and the slope was around 3 to 4 s/(100 µg/l). The results of the PK/PD analyses in Phase II were consistent with the data established in healthy subjects.

In patients receiving rivaroxaban 20 mg once daily for treatment of acute DVT, the geometric mean concentration (90% interval) at 2 - 4 h and about 24 h after dose (roughly representing maximum and minimum concentrations during the dose interval) was 215 (22 - 535) and 32 (6 - 239) µg/l, respectively.

Paediatric population
Safety and efficacy have not been established in the indication prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation for children and adolescents up to 18 years.

Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, single dose toxicity, phototoxicity, genotoxicity, carcinogenic potential and reproductive toxicity.

Effects observed in repeat-dose toxicity studies were mainly due to the exaggerated pharmacodynamic activity of rivaroxaban. In rats, increased IgG and IgA plasma levels were seen at clinically relevant exposure levels.

In rats, no effects on male or female fertility were seen. Animal studies have shown reproductive toxicity related to the pharmacological mode of action of rivaroxaban (e.g. haemorrhagic complications). Embryo-foetal toxicity (post-implantation loss, retarded/progressed ossification, hepatic multiple light coloured spots) and an increased incidence of common malformations as well as placental changes were observed at clinically relevant plasma concentrations. In the pre- and post-natal study in rats, reduced viability of the offspring was observed at doses that were toxic to the dams.

Rivaroxaban was tested in juvenile rats up to 3-month treatment duration starting at postnatal day 4 showing a non dose-related increase in periinsular haemorrhage. No evidence of target organ- specific toxicity was seen.

CLINICAL PARTICULARS

Indications

Adults
Xabarem is indicated for prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

There are limited data on the relative effectiveness of rivaroxaban and warfarin in reducing the risk of stroke and systemic embolism when warfarin therapy is well-controlled *(see section 'Pharmacodynamic properties').*

Xabarem is indicated for the treatment of Deep Vein Thrombosis (DVT) and pulmonary embolism (PE), and for the prevention of recurrent DVT, PE in adults. *(See section 'Warnings and precautions'*

for haemodynamically unstable PE patients.)

Paediatric population

Xabarem 15 mg
Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years and weighing from 30kg to 50 kg after at least 5 days of initial parenteral anticoagulation treatment.

Xabarem 20 mg
Treatment of venous thromboembolism (VTE) and prevention of VTE recurrence in children and adolescents aged less than 18 years and weighing more than 50 kg after at least 5 days of initial parenteral anticoagulation treatment.

Dosage and method of administration

Posology

Prevention of stroke and systemic embolism in adults
The recommended dose is 20 mg once daily, which is also the recommended maximum dose.

If a dose is missed the patient should take Xabarem immediately and continue on the following day with the once daily intake as recommended. The dose should not be doubled within the same day to make up for a missed dose.

Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE in adults
The recommended dose for the initial treatment of acute DVT or PE is 15 mg twice daily for the first three weeks followed by 20 mg once daily for the continued treatment and prevention of recurrent DVT and PE.

Short duration of therapy (at least 3 months) should be considered in patients with DVT or PE provoked by major transient risk factors (i.e. recent major surgery or trauma). Longer duration of therapy should be considered in patients with provoked DVT or PE not related to major transient risk factors, unprovoked DVT or PE, or a history of recurrent DVT or PE.

When extended prevention of recurrent DVT and PE is indicated (following completion of at least 6 months therapy for DVT or PE), the recommended dose is 10 mg once daily. In patients in whom the risk of recurrent DVT or PE is considered high, such as those with complicated comorbidities, or who have developed recurrent DVT or PE on extended prevention with Xabarem 10 mg once daily, a dose of Xabarem 20 mg once daily should be considered.

The duration of therapy and dose selection should be individualised after careful assessment of the treatment benefit against the risk for bleeding *(see section 'Warnings and precautions').*

	Time Period	Dosing schedule	Maximum daily dose
Treatment and prevention of recurrent DVT and PE	Day 1-21	15 mg twice daily	30 mg
	Day 22 onwards	20 mg once daily	20 mg

Prevention of recurrent DVT and PE	Following completion of at least 6 months therapy for DVT or PE	10 mg once daily or 20 mg once daily	10 mg or 20 mg

It is essential to adhere to the dosage schedule provided.

If a dose is missed during the 15 mg twice daily treatment phase, the patient should take Xabarem immediately to ensure intake of 30 mg Xabarem per day. In this case two 15 mg tablets may be taken at once. The patient should continue with the regular 15 mg twice daily intake as recommended on the following day.

If a dose is missed during the once daily treatment phase, the patient should take Xabarem immediately to ensure intake of the recommended daily dose. The patient should continue with the regular once daily dose intake as recommended on the following day.

Treatment of VTE and prevention of VTE recurrence in children and adolescents
Xabarem treatment in children and adolescents aged less than 18 years should be initiated following at least 5 days of initial parenteral anticoagulation treatment *(see section 'Pharmacodynamic properties').*
The dose for children and adolescent is calculated based on body weight.

- Body weight of 50 kg or more: a once daily dose of 20 mg rivaroxaban is recommended. This is the maximum daily dose.
- Body weight from 30 to 50 kg: a once daily dose of 15 mg rivaroxaban is recommended. This is the maximum daily dose.
- For patients with body weight less 30 kg refer to the PI of rivaroxaban granules for oral suspension.

The weight of a child should be monitored and the dose reviewed regularly. This is to ensure a therapeutic dose is maintained. Dose adjustments should be made based on changes in body weight only.

Treatment should be continued for at least 3 months in children and adolescents. Treatment can be extended up to 12 months when clinically necessary. There is no data available in children to support a dose reduction after 6 months treatment. The benefit-risk of continued therapy after 3 months should be assessed on an individual basis taking into account the risk for recurrent thrombosis versus the potential bleeding risk.

If a dose is missed, the missed dose should be taken as soon as possible after it is noticed, but only on the same day. If this is not possible, the patient should skip the dose and continue with the next dose as prescribed. The patient should not take two doses to make up for a missed dose.

Intake of Xabarem in relation to food
Xabarem 15 mg and Xabarem 20 mg tablets are to be taken with food *(see section 'Pharmacokinetic properties').*

Converting from Vitamin K Antagonists (VKA) to Xabarem
- Prevention of stroke and systemic embolism:

VKA treatment should be stopped and Xabarem therapy should be initiated when the INR is ≤ 3.0.

- Treatment of DVT, PE and prevention of recurrence in adults and treatment of VTE and prevention of recurrence in paediatric patients:
  VKA treatment should be stopped and Xabarem therapy should be initiated once the INR is ≤ 2.5.

When converting patients from VKAs to Xabarem, INR values will be falsely elevated after the intake of Xabarem. The INR is not valid to measure the anticoagulant activity of Xabarem, and therefore should not be used *(see section 'Interaction')*.

Converting from Xabarem to Vitamin K antagonists (VKA)
There is a potential for inadequate anticoagulation during the transition from Xabarem to VKA. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that Xabarem can contribute to an elevated INR.

No clinical trial data are available to guide converting patients from rivaroxaban to warfarin. Rivaroxaban affects INR, so INR measurements made during co-administration with warfarin may not be useful for determining the appropriate dose of warfarin.

One approach is to discontinue Xabarem and begin both a parenteral anticoagulant and warfarin at the time the next dose of Xabarem would have been taken.
In another approach, in patients converting from Xabarem to VKA, VKA should be given concurrently until the INR is ≥2.0. For the first two days of the conversion period, standard VKA dosing should be used followed by VKA dosing guided by INR testing. While patients are on both Xabarem and VKA, the INR should not be tested earlier than 24 h (after the previous dose but prior to the next dose of Xabarem). Once Xabarem is discontinued INR testing may be done reliably 24 h after the last dose *(see sections 'Interactions' and 'Pharmacokinetic properties')*. Patients are to be carefully monitored for signs of bleeding complications during the conversion period.

Paediatric patients:
Children who convert from Xabarem to VKA need to continue Xabarem for 48 hours after the first dose of VKA. After 2 days of co-administration an INR should be obtained prior to the next scheduled dose of Xabarem. Co-administration of Xabarem and VKA is advised to continue until the INR is ≥ 2.0. Once Xabarem is discontinued INR testing may be done reliably 24 hours after the last dose (*see above and section 'Interactions'*).

Converting from parenteral anticoagulants to Xabarem
For adult and paediatric patients currently receiving a parenteral anticoagulant, start Xabarem 0 to 2 hours before the time of the next scheduled administration of the parenteral drug (e.g. LMWH) or at the time of discontinuation of a continuously administered parenteral drug (e.g. intravenous unfractionated heparin).

Converting from Xabarem to parenteral anticoagulants
Discontinue Xabarem and give the first dose of parenteral anticoagulant at the time the next Xabarem dose would be taken.

Cardioversion

Xabarem can be initiated or continued in patients who may require cardioversion.
For transesophageal echocardiogram (TEE) guided cardioversion in patients not previously treated with anticoagulants, Xabarem treatment should be started at least 4 hours before cardioversion to ensure adequate anticoagulation *(see sections 'Pharmacodynamic properties' and 'Pharmacokinetic properties').*

Additional information on special populations

Patients with renal impairment
Adults:
Limited clinical data for patients with severe renal impairment (creatinine clearance 15 - 29 ml/min) indicate that rivaroxaban plasma concentrations are significantly increased. Therefore, Xabarem is to be used with caution in these patients. Use is not recommended in patients with creatinine clearance < 15 ml/min *(see sections 'Warnings and precautions' and 'Pharmacokinetic properties').*

In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15 - 29 ml/min) renal impairment the following dosage recommendations apply:

- For the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation, the recommended dose is 15 mg once daily *(see section 'Pharmacokinetic properties').*

- For the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE: patients should be treated with 15 mg twice daily for the first 3 weeks. Thereafter, when the recommended dose is 20 mg once daily, a reduction of the dose from 20 mg once daily to 15 mg once daily should be considered if the patient's assessed risk for bleeding outweighs the risk for recurrent DVT and PE. The recommendation for the use of 15 mg is based on PK modelling and has not been studied in this clinical setting *(see sections 'Warnings and precautions', 'Pharmacodynamic properties' and 'Pharmacokinetic properties').*
  When the recommended dose is 10 mg once daily, no dose adjustment from the recommended dose is necessary.

No dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50 - 80 ml/min) *(see section 'Pharmacokinetic properties').*

Paediatric population:
- Children and adolescents with mild renal impairment (glomerular filtration rate 50 - 80 mL/min/1.73 m2): no dose adjustment is required, based on data in adults and limited data in paediatric patients *(see section 'Pharmacokinetic properties')*.
- Children and adolescents with moderate or severe renal impairment (glomerular filtration rate <50 mL/min/1.73 m2): Xabarem is not recommended as no clinical data is available *(see section 'Warnings and precautions').*

Patients with hepatic impairment
Xabarem is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C *(see sections*

'Contraindications' and 'Pharmacokinetic properties').
No clinical data is available in children with hepatic impairment.

Geriatric patients
No dose adjustment.

Body weight
No dose adjustment for adults.

For paediatric patients the dose is determined based on body weight.

Gender
No dose adjustment.

Children and adolescents
The safety and efficacy of rivaroxaban in children aged 0 to < 18 years have not been established in the indication prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation. No data are available. Therefore, it is not recommended for use in children below 18 years of age in indications other than the treatment of VTE and prevention of VTE recurrence.

SPAF: Patients who undergo PCI (percutaneous coronary intervention) with stent placement
There is limited experience of a reduced dose of 15mg Xabarem once daily (or 10mg Xabarem once daily for patients with moderate renal impairment [creatinine clearance 30 - 49 ml/min]) in addition to a P2Y12 inhibitor for a maximum of 12 months in patients with non-valvular atrial fibrillation who require oral anticoagulation and undergo PCI with stent placement *(see section 'Warning and precautions', 'Pharmacodynamic properties').*

Method of administration
Adults
For oral use.

Crushing of tablets
For patients who are unable to swallow whole tablets, Xabarem tablet may be crushed and mixed with water or soft foods such as applesauce immediately prior to use and administered orally. After the administration of crushed Xabarem 15 mg or Xabarem 20 mg tablets, the dose should be immediately followed by food.

The crushed Xabarem tablet may be given through gastric tubes. Gastric placement of the tube should be confirmed before administering Xabarem. The crushed tablet should be administered in a small amount of water via a gastric tube after which it should be flushed with water. After the administration of crushed Xabarem15 mg or 20 mg tablets, the dose should then be immediately followed by enteral feeding *(see section 'Pharmacokinetic properties').*

Children and adolescents weighing 30 kg to 50 kg
Xabarem is for oral use.
The patient should be advised to swallow the tablet with liquid. It should also be taken with food *(see section 'Pharmacokinetic properties')*. The tablets should be taken approximately 24 hours apart.

In case the patient immediately spits up the dose or vomits within 30 minutes after receiving the dose, a new dose should be given. However, if the patient vomits more than 30 minutes after the dose, the dose should not be re-administered and the next dose should be taken as scheduled.

The tablet must not be split in an attempt to provide a fraction of a tablet dose.

Crushing of tablets
For patients who are unable to swallow whole tablets, rivaroxaban granules for oral suspension should be used. If the oral suspension is not immediately available, when doses of 15 mg or 20 mg rivaroxaban are prescribed, these could be provided by crushing the 15 mg or 20 mg tablet and mixing it with water or apple puree immediately prior to use and administering orally.
The crushed tablet may be given through a nasogastric or gastric feeding tube *(see sections 'Pharmacokinetic properties').*

Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Clinically significant active bleeding.

Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C *(see section 'Pharmacokinetic properties').*

Pregnancy and lactation *(see section 'Pregnancy and lactation').*

Lesion or condition if considered to be a significant risk of major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities.

Concomitant treatment with any other anticoagulant agent e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, apixaban, dabigatran, etc.) except under the circumstances of switching therapy to or from rivaroxaban *(see section 'Dosage and method of administration')* or when UFH is given at doses necessary to maintain an open central venous or arterial catheter. *(see section 'Interactions').*

Warnings and precautions

Increased Risk of Stroke after Discontinuation in Nonvalvular Atrial Fibrillation
Discontinuing Xabarem in the absence of adequate alternative anticoagulation increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from rivaroxaban to warfarin in clinical trials in atrial fibrillation patients. If Xabarem must be discontinued for a reason other than pathological bleeding, consider administering another anticoagulant *(see sections 'Dosage and method of administration' and 'Pharmacodynamic properties').*

Haemorrhagic risk
As with other anticoagulants, patients taking Xabarem are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. Xabarem administration should be discontinued if severe haemorrhage occurs.

In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary) and anemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate.

Several sub-groups of patients, as detailed below, are at increased risk of bleeding. These patients are to be carefully monitored for signs of bleeding complications after initiation of treatment. Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

Although treatment with rivaroxaban does not require routine monitoring exposure, rivaroxaban levels measured with a calibrated quantitative anti-Factor Xa assay may be useful in exceptional situations where knowledge of rivaroxaban exposure may help to inform clinical decisions, e.g. overdose and emergency surgery *(see section 'Pharmacodynamic properties' and 'Pharmacokinetic properties').*

Paediatric population
There is limited data in children with cerebral vein and sinus thrombosis who have a CNS infection *(see section 'Pharmacodynamic properties')*. The risk of bleeding should be carefully evaluated before and during therapy with rivaroxaban.

Renal impairment
In adult patients with severe renal impairment (creatinine clearance < 30 ml/min) rivaroxaban plasma levels may be significantly increased (1.6 fold on average) which may lead to an increased bleeding risk. Use is not recommended in patients with creatinine clearance < 15 ml/min. Xabarem is to be used with caution in patients with creatinine clearance 15 - 29 ml/min. *(see sections 'Dosage and method of administration' and 'Pharmacokinetic properties').*

Xabarem should be used with caution in patients with renal impairment concomitantly receiving other medicinal products that are potent inhibitors of CYP3A4 (e.g. clarithromycin, telithromycin) as PK modelling shows increased rivaroxaban concentrations in these patients.
Xabarem is not recommended in children and adolescents with moderate or severe renal impairment (glomerular filtration rate < 50 mL/min/1.73 m^2), as no clinical data is available.

Elderly population
Increasing age may increase haemorrhagic risk *(see section 'Pharmacokinetic properties').*

Patients with high risk triple positive antiphospholipid syndrome
Xabarem is not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome and are persistently triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti–beta 2-glycoprotein I antibodies) as treatment with rivaroxaban is associated with an increased rate of recurrent thrombotic events compared with vitamin K antagonists (VKA).

Concomitant medication
The use of Xabarem is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir). These active substances are strong inhibitors of both CYP3A4 and P-gp and therefore may increase rivaroxaban plasma concentrations to a clinically relevant degree (2.6 fold on average) which may lead to an increased bleeding risk. No clinical data is available in children receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp *(see section 'Interactions').*

The azole antimycotic fluconazole, a moderate CYP3A4 inhibitor, has however less effect on rivaroxaban exposure and can be co-administered *(see section 'Interactions').*

Care is to be taken if patients are treated concomitantly with medicinal products affecting haemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid, platelet aggregation inhibitors, other antithrombotic agents, or selective serotonin reuptake inhibitors (SSRI), and serotonin norepinephrine reuptake inhibitors (SNRIs), *(see section 'Interactions').*

For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered *(see section 'Interactions').*

Bleeding risk
Rivaroxaban, like other antithrombotic agents, is to be used with caution in patients with an increased bleeding risk such as:
- congenital or acquired bleeding disorders.
- uncontrolled severe arterial hypertension.
- active ulcerative gastrointestinal disease.
- vascular retinopathy.
- bronchiectasis or history of pulmonary bleeding.

Bleeding during antithrombotic treatment may unmask underlying yet unknown malignancy, in particular in the gastrointestinal or genitourinary tract. Patients with malignant disease may simultaneously be at higher risk of bleeding and thrombosis. The individual benefit of antithrombotic treatment should be weighed against risk for bleeding in patients with active cancer dependent on tumor location, antineoplastic therapy and stage of disease.

Patients with prosthetic valves
Xabarem is not recommended for thromboprohylaxis in patients having recently undergone transcatheter aortic valve replacement (TAVR) based on data from a randomized controlled clinical study comparing rivaroxaban-regimen to an antiplatelet regimen.

The safety and efficacy of rivaroxaban have not been studied in patients with other prosthetic heart valves or other valve procedures; therefore, there are no data to support that rivaroxaban 20 mg (15 mg in patients with moderate renal impairment) provides adequate anticoagulation in those patient populations. Treatment with Xabarem is not recommended for these patients.

Surgery and interventions
If an invasive procedure or surgical intervention is required, Xabarem should be stopped at least 24

hours before the intervention, if possible and based on the clinical judgment of the physician. If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.

Xabarem should be restarted as soon as possible after the invasive procedure or surgical intervention provided the clinical situation allows and adequate haemostasis has been established *(see section 'Pharmacokinetic properties').*

Neuraxial (epidural/spinal) anaesthesia
When neuraxial (epidural/spinal) anaesthesia or spinal puncture is performed, patients treated with antithrombotics for prevention of thromboembolic complications are at risk for development of an epidural or spinal haematoma which may result in long-term or permanent paralysis.

The risk of these events is even further increased by use of indwelling epidural catheters or the concomitant use of drugs affecting haemostasis. The risk may also be increased by traumatic or repeated epidural or spinal puncture.

Patients should be frequently monitored for signs and symptoms of neurological impairment (eg. numbness or weakness of the legs, bowel or bladder dysfunction). If neurological deficits are noted, urgent diagnosis and treatment is necessary.

The physician should consider the potential benefit versus the risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thrombopropylaxis.

There is no clinical experience with the use of 15mg and 20mg rivaroxaban in these situations.

To reduce the potential risk of bleeding associated with the concurrent use of rivaroxaban and neuraxial (epidural/spinal) anesthesia or spinal puncture, consider the pharmacokinetic profile of rivaroxaban. Placement or removal of an epidural catheter or lumbar puncture is best performed when the anticoagulant effect of rivaroxaban is estimated to be low. However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known and should be weighed against the urgency of a diagnostic procedure.

For removal of an epidural catheter and based on the general PK characteristics at least 2 x half- life should elapse, i.e. at least 18 hours in young adult patients and 26 hours in elderly patients, after the last administration of Xabarem *(see section 'Pharmacokinetic Properties').*

Xabarem should be administered at earliest 6 hours after the removal of the catheter.

If traumatic puncture occurs the administration of Xabarem should be delayed for 24 hours.
No data is available on the timing of the placement or removal of neuraxial catheter in children while on Xabarem. In such cases, discontinue rivaroxaban and consider a short acting parenteral anticoagulant.

Interaction with CYP3A4 inducers
The concomitant use of rivaroxaban with strong CYP3A4 inducers (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital or St. John's Wort) may lead to reduced rivaroxaban plasma

concentrations. Strong CYP3A4 inducers should be co-administered with caution *(see section 'Interactions').*

Information about excipients
Xabarem contains lactose
Patients with rare hereditary problems of galactose intolerance, lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

Xabarem contains sodium
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium-free".

Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy
Xabarem is not recommended as an alternative to unfractionated heparin in patients with pulmonary embolism who are haemodynamically unstable or may receive thrombolysis or pulmonary embolectomy since the safety and efficacy of rivaroxaban have not been established in these clinical situations.

SPAF: Patients who undergo PCI with stent placement
Clinical data are available from an interventional study with the primary objective to assess safety in patients with non-valvular atrial fibrillation who undergo PCI with stent placement. Data on efficacy in this population are limited *(see section 'Dosage and method of administration', 'Pharmacodynamic properties')*. No data are available for such patients with a history of stroke/transient ischaemic attack (TIA).

Interactions

The extent of interactions in the paediatric population is not known. The below mentioned interaction data was obtained in adults and the warnings in section '*Warnings and precautions*' should be taken into account for the paediatric population.

CYP3A4 and P-gp inhibitors
Co-administration of rivaroxaban with ketoconazole (400 mg once a day [od]) or ritonavir (600 mg twice a day [bid]) led to a 2.6 fold / 2.5 fold increase in mean rivaroxaban AUC and a 1.7 fold / 1.6 fold increase in mean rivaroxaban C_{max}, with significant increases in pharmacodynamic effects which may lead to an increased bleeding risk. Therefore, the use of Xabarem is not recommended in patients receiving concomitant systemic treatment with azole- antimycotics such as ketoconazole, itraconazole, voriconazole and posaconazole or HIV protease inhibitors. These active substances are strong inhibitors of both CYP3A4 and P-gp *(see section 'Warnings and precautions').*

Active substances strongly inhibiting only one of the rivaroxaban elimination pathways, either CYP3A4 or P-gp, are expected to increase rivaroxaban plasma concentrations to a lesser extent. Clarithromycin (500 mg bid), for instance, considered as a strong CYP3A4 inhibitor and moderate P-gp inhibitor, led to a 1.5 fold increase in mean rivaroxaban AUC and a 1.4 fold increase in C_{max}. This increase is not considered clinically relevant.

Erythromycin (500 mg three times a day [tid]), which inhibits CYP3A4 and P-gp moderately, led to a 1.3 fold increase in mean rivaroxaban AUC and C_{max}. This increase is not considered clinically relevant.

In subjects with mild renal impairment, erythromycin (500 mg three times a day) led to a 1.8-fold increase in mean rivaroxaban AUC and 1.6-fold increase in C_{max} when compared to subjects with normal renal function without co-medication. In subjects with moderate renal impairment, erythromycin led to a 2.0-fold increase in mean rivaroxaban AUC and 1.6-fold increase in C_{max} when compared to subjects with normal renal function without co-medication *(see section 'Warnings and precautions').*

Fluconazole (400 mg once daily), considered as a moderate CYP3A4 inhibitor, led to a 1.4 fold increase in mean rivaroxaban AUC and a 1.3 fold increase in mean C_{max}. This increase is not considered clinically relevant *(see section 'Warnings and precautions').*

Anticoagulants
After combined administration of enoxaparin (40 mg single dose) with rivaroxaban (10 mg single dose) an additive effect on anti-Factor Xa activity was observed without any additional effects on clotting tests (PT, aPTT). Enoxaparin did not affect the pharmacokinetics of rivaroxaban.
Due to the increased bleeding risk care is to be taken if patients are treated concomitantly with any other anticoagulants *(see section 'Warnings and precautions').*

NSAIDs/platelet aggregation inhibitors
No clinically relevant prolongation of bleeding time was observed after concomitant administration of rivaroxaban (15 mg) and 500 mg naproxen. Nevertheless, there may be individuals with a more pronounced pharmacodynamic response.

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with 500 mg acetylsalicylic acid.

Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) did not show a pharmacokinetic interaction with rivaroxaban (15 mg) but a relevant increase in bleeding time was observed in a subset of patients which was not correlated to platelet aggregation, P-selectin or GPIIb/IIIa receptor levels.

Care is to be taken if patients are treated concomitantly with NSAIDs (including acetylsalicylic acid) and platelet aggregation inhibitors because these medicinal products typically increase the bleeding risk *(see section 'Warnings and precautions').*

SSRIs/SNRIs
As with other anticoagulants the possibility may exist that patients are at increased risk of bleeding in case of concomitant use with SSRIs or SNRIs due to their reported effect on platelets. When concomitantly used in the rivaroxaban clinical program, numerically higher rates of major or non-major clinically relevant bleeding were observed in all treatment groups.

Warfarin
Converting patients from the vitamin K antagonist warfarin (INR 2.0 to 3.0) to rivaroxaban (20 mg) or

from rivaroxaban (20 mg) to warfarin (INR 2.0 to 3.0) increased prothrombin time/INR (Neoplastin) more than additively (individual INR values up to 12 may be observed), whereas effects on aPTT, inhibition of factor Xa activity and endogenous thrombin potential were additive.

If it is desired to test the pharmacodynamic effects of rivaroxaban during the conversion period, anti-factor Xa activity, PiCT, and Heptest can be used as these tests were not affected by warfarin. On the fourth day after the last dose of warfarin, all tests (including PT, aPTT, inhibition of factor Xa activity and ETP) reflected only the effect of rivaroxaban.

If it is desired to test the pharmacodynamic effects of warfarin during the conversion period, INR measurement can be used at the C_{trough} of rivaroxaban (24 hours after the previous intake of rivaroxaban) as this test is minimally affected by rivaroxaban at this time point.

No pharmacokinetic interaction was observed between warfarin and rivaroxaban.

CYP3A4 inducers
Co-administration of rivaroxaban with the strong CYP3A4 inducer rifampicin led to an approximate 50 % decrease in mean rivaroxaban AUC, with parallel decreases in its pharmacodynamic effects. The concomitant use of rivaroxaban with other strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbital or St. John's Wort) may also lead to reduced rivaroxaban plasma concentrations. Strong CYP3A4 inducers should be co-administered with caution *(see section 'Pharmacokinetic properties').*

Other concomitant therapies
No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with midazolam (substrate of CYP3A4), digoxin (substrate of P-gp), atorvastatin (substrate of CYP3A4 and P-gp) or omeprazole (proton pump inhibitor). Rivaroxaban neither inhibits nor induces any major CYP isoforms like CYP3A4.

Food and dairy products
Xabarem 20 mg film-coated tablets are to be taken with food *(see sections 'Dosage and method of administration' and 'Pharmacokinetic properties').*

Interaction with laboratory parameters
Clotting parameters (e.g. PT, aPTT, HepTest) are affected as expected by the mode of action of rivaroxaban (*see section 'Pharmacodynamic properties').*

Pregnancy and lactation

Fertility
No specific studies with rivaroxaban in humans have been conducted to evaluate effects on fertility. In a study on male and female fertility in rats no effects were seen *(see section 'Preclinical safety data').*

Pregnancy
Safety and efficacy of rivaroxaban have not been established in pregnant women. Studies in animals have shown reproductive toxicity *(see section 'Preclinical safety data').* Due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, Xabarem is contraindicated during pregnancy *(see section 'Contraindications').*

Women of child-bearing potential should avoid becoming pregnant during treatment with rivaroxaban.

Lactation
Safety and efficacy of rivaroxaban have not been established in nursing mothers. Data from animals indicate that rivaroxaban is secreted into milk. Therefore, Xabarem is contraindicated during breast feeding *(see section 'Contraindications').* A decision must be made whether to discontinue breast feeding or to discontinue/abstain from therapy.

Effects on ability to drive and use machines

Syncope and dizziness have been reported and may affect the ability to drive and use machines. These adverse reactions have been reported to be common *(see section 'Adverse effects')*. Patients experiencing these adverse reactions should not drive or use machines.

Adverse effects

Summary of the safety profile
The safety of rivaroxaban has been evaluated in thirteen phase III studies in adults including 53,103 patients exposed to rivaroxaban and in two phase II and one phase III paediatric studies including 412 patients. See phase III studies as listed in table 10.

Table 10: Number of patients studied, total daily dose and maximum treatment duration in the rivaroxaban adult and paediatric phase III studies

Indication	Number of patients	Maximum daily dose	Maximum treatment duration
Prevention of venous thromboembolism in medically ill patients	3,997	10mg	39 days
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	6,097	10 mg	39 days
Treatment of DVT, PE and prevention of recurrent DVT, PE	6790	Day 1-21: 30 mg Day 22 and onwards: 20 mg After at least six months: 10 mg or 20 mg	21 months
Treatment of VTE and prevention of VTE recurrence in term neonates and children aged less than 18 years following initiation of standard anticoagulation treatment	329	Body weight adjusted dose to achieve a similar exposure as that observed in adults treated for DVT with 20 mg rivaroxaban once daily	12 months
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	7,750	20 mg	41 months

Prevention of cardiovascular death, MI or stroke events in patients after an acute coronary syndrome (ACS)	10,225	5 mg or 10 mg respectively, in combination with ASA or ASA plus clopidogrel or ticlopidine	31 months
Prevention of stroke, myocardial infarction and cardiovascular death, and prevention of acute limb ischemia and mortality in patients with CAD or PAD	18,244	5 mg in combination with 100 mg ASA or 10 mg alone	47 months

*Patients exposed to at least one dose of rivaroxaban

Table 11: Bleeding and anemia events rates in patients exposed to rivaroxaban across the completed adult and paediatric phase III studies

Indication	Any Bleeding	Anemia
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	6.8% of patients	5.9% of patients
Prevention of venous thromboembolism in medically ill patients	12.6% of patients	2.1% of patients
Treatment of DVT, PE and prevention of recurrent DVT, PE	23% of patients	1.6% of patients
Treatment of VTE and prevention of VTE recurrence in term neonates and children aged less than 18 years following initiation of standard anticoagulation treatment	39.5% of patients	4.6% of patients
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	28 per 100 patient years	2.5 per 100 patient years
Prevention of cardiovascular events in patients after an ACS	22 per 100 patient years	1.4 per 100 patient years
Prevention of stroke, myocardial infarction and cardiovascular death, and prevention of acute limb ischemia and mortality in patients with CAD or PAD	6.7 per 100 patient years	0.15 per 100 patient years*

* A pre-specified selective approach to adverse event collection was applied.

Tabulated list of adverse reactions

The frequencies of adverse reactions reported with rivaroxaban in adult and paediatric patients are summarized in table 3 below by system organ class (in MedDRA) and by frequency.

Frequencies are defined as:
common (≥ 1/100 to < 1/10)
uncommon (≥ 1/1,000 to < 1/100)
rare (≥ 1/10,000 to < 1/1,000)
Not known: cannot be estimated from the available data.

Table 12: All treatment-emergent adverse reactions reported in adult patients in phase III studies and in two phase II and one phase III studies in paediatric patients

Common	Uncommon	Rare	Not known
Blood and lymphatic system disorders			
Anaemia (incl. respective laboratory parameters)	Thrombocytosis (incl. platelet count increased)[A]		
Immune system disorders			
	Allergic reaction, dermatitis allergic		
Nervous system disorders			
Dizziness, headache	Cerebral and intracranial haemorrhage, syncope		
Eye disorders			
Eye haemorrhage (incl. conjunctival haemorrhage)			
Cardiac disorders			
	Tachycardia		
Vascular disorders			
Hypotension, haematoma			
Respiratory, thoracic and mediastinal disorders			
Epistaxis, haemoptysis			
Gastrointestinal disorders			
Gingival bleeding, gastrointestinal tract haemorrhage (incl. rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation[A], diarrhoea, vomiting[A]	Dry mouth		
Hepatobiliary disorders			
	Hepatic impairment	Jaundice	
Skin and subcutaneous tissue disorders			
Pruritus (incl. uncommon cases of generalized pruritus), rash, ecchymosis, cutaneous and subcutaneous haemorrhage	Urticaria		
Musculoskeletal and connective tissue disorders			

Pain in extremity[A]	Haemarthrosis	Muscle haemorrhage	Compartment syndrome secondary to a bleeding
Renal and urinary disorders			
Urogenital tract haemorrhage (incl. haematuria and menorrhagia[B]), renal impairment (incl. blood creatinine increased, blood urea increased)[A]			Renal failure/acute renal failure secondary to a bleeding sufficient to cause hypoperfusion
General disorders and administration site conditions			
Fever[A], peripheral oedema, decreased general strength and energy (incl. fatigue and asthenia)	Feeling unwell (incl. malaise)	Localised oedema[A]	
Investigations			
Increase in transaminases	Increased bilirubin, increased blood alkaline phosphatase[A], increased LDHA, increased lipase[A], increased amylase[A], increased GGTA	Bilirubin conjugated increased (with or without concomitant increase of ALT)	
Injury, poisoning and procedural complications			
Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage), Contusion	Wound secretion[A]	Vascular pseudoaneurysm[C]	

A: observed in prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery;
B: observed in treatment of DVT, PE and prevention recurrence as very common in women <55 years.
C: observed as uncommon in prevention of cardiovascular death in patients after an ACS (following percutaneous intervention).
< ADR term representation is based on MedDRA version 20.0 >

Description of selected adverse reactions

Due to the pharmacological mode of action, the use of rivaroxaban may be associated with an increased risk of occult or overt bleeding from any tissue or organ which may result in post haemorrhagic anaemia. The signs, symptoms, and severity (including fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anaemia *(see section 'Management of bleeding')*. In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary) and anemia were seen more frequently during long term rivaroxaban treatment compared with VKA treatment. Thus, in addition to adequate clinical surveillance,

laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate. The risk of bleedings may be increased in certain patient groups e.g. those patients with uncontrolled severe arterial hypertension and/or on concomitant treatment affecting haemostasis (see Haemorrhagic risk in section 4.4). Menstrual bleeding may be intensified and/or prolonged. Haemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnoea, and unexplained shock. In some cases as a consequence of anaemia, symptoms of cardiac ischaemia like chest pain or angina pectoris have been observed. Known complications secondary to severe bleeding such as compartment syndrome and renal failure due to hypoperfusion have been reported for rivaroxaban. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

Paediatric population
The safety assessment in children and adolescents is based on the safety data from two phase II and one phase III open-label active controlled studies in paediatric patients aged birth to less than 18 years.

The safety findings were generally similar between rivaroxaban and comparator in the various paediatric age groups. Overall, the safety profile in the 412 children and adolescents treated with rivaroxaban was similar to that observed in the adult population and consistent across age subgroups, although assessment is limited by the small number of patients.

In paediatric patients, headache (very common, 16.7%), fever (very common, 11.7%), epistaxis (very common, 11.2%), vomiting (very common, 10.7%), tachycardia (common, 1.5%), increase in bilirubin (common, 1.5%) and bilirubin conjugated increased (uncommon, 0.7%) were reported more frequently as compared to adults. Consistent with adult population, menorrhagia was observed in 6.6% (common) of female adolescents after menarche. Thrombocytopenia as observed in the post-marketing experience in adult population was common (4.6%) in paediatric clinical studies. The adverse drug reactions in paediatric patients were primarily mild to moderate in severity.

Post marketing observations
The following adverse reactions have been reported post-marketing in temporal association with the use of rivaroxaban. The frequency of these adverse reactions reported from post-marketing experience cannot be estimated.

Immune system disorders: Angioedema and allergic oedema (In the pooled phase III trials, these events were uncommon (≥ 1/1,000 to < 1/100)).

Injury, poisoning and procedural complications: Splenic rupture (In the pooled phase III trials, these events were very rare (< 1/10,000)).
Hepatobiliary disorders: Cholestasis, Hepatitis (incl. hepatocellular injury) (In the pooled phase III trials, these events were rare (≥ 1/10,000 to < 1/1,000)).

Blood and lymphatic system disorders: Thrombocytopenia (In the pooled phase III trials, these events were uncommon (≥ 1/1,000 to < 1/100)); agranulocytosis
Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome.

Renal and urinary disorders: Anticoagulant-related nephropathy (In the pooled phase III trials, the frequency cannot be estimated).

Respiratory, thoracic and mediastinal disorders: Eosinophilic pneumonia (In the pooled phase III trials, these events were very rare (<1/10,000)).

Overdose

In adults, rare cases of overdose up to 600 mg have been reported without bleeding complications or other adverse reactions. There is limited data available in children. Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg rivaroxaban or above in adults, however, no data is available at supratherapeutic doses in children.
A specific antidote antagonising the pharmacodynamic effect of rivaroxaban is not available.
The use of activated charcoal to reduce absorption in case of rivaroxaban overdose may be considered.

Management of Bleeding
Should a bleeding complication arise in a patient receiving rivaroxaban, the next rivaroxaban administration should be delayed or treatment should be discontinued as appropriate.
Rivaroxaban has a half-life of approximately 5 to 13 hours in adults. The half life in children estimated using population pharmacokinetic (popPK) modelling approaches is shorter *(see section 'Pharmacokinetic properties')*. Management should be individualised according to the severity and location of the haemorrhage. Appropriate symptomatic treatment could be used as needed, such as mechanical compression (e.g. for severe epistaxis), surgical haemostasis with bleeding control procedures, fluid replacement and haemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets.
If bleeding cannot be controlled by the above measures, administration of a specific procoagulant reversal agent should be considered, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa). However, there is currently very limited clinical experience with the use of these products in adults and in children receiving rivaroxaban. *(see section 'Pharmacodynamic properties')* The recommendation is also based on limited non-clinical data. Re-dosing of recombinant factor VIIa shall be considered and titrated depending on improvement of bleeding.

Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. There is limited experience with tranexamic acid and no experience with aminocaproic acid and aprotinin in adults receiving rivaroxaban. There is no experience on the use of these agents in children receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with the use of systemic haemostatic desmopressin in individuals receiving rivaroxaban. Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

PHARMACEUTICAL PARTICULARS

List of excipients

Tablet core
Microcrystalline cellulose PH102 (E460)
Microcrystalline cellulose M200 (E460)

Croscarmellose sodium (E468)
Lactose monohydrate
Hypromellose HPMC 2910(E464)
Sodium laurilsulfate
Magnesium stearate vegetable (E470b)

Coating
Macrogol (E1521)
Hypromellose HPMC 2910 (E464)
Titanium dioxide (E 171)
Iron oxide red (E 172)

Shelf life

3 years.

Crushed tablets
Crushed rivaroxaban tablets are stable in water and in apple puree for up to 4 hours.

Storage conditions

Do not store above 30 ºC.

Keep out of the reach and sight of children.

Presentation

Cardboard box containing aluminium- PVC/PVDC blisters, of 10 film-coated tablets.
Pack size of 30 film-coated tablets.

Manufacturer

Remedica Ltd.
Aharnon Str., Limassol Industrial Estate, 3056 Limassol, Cyprus

Product registrant

Goldplus Universal Pte Ltd
103 Kallang Avenue #06-02, Singapore 339504

Date of revision of the text

For internal use only: sg-pi-xabarem-15mg-20mg-fc-tabs-a4