INVAROX FILM-COATED TABLET 10 MG

1. NAME OF THE MEDICINAL PRODUCT

INVAROX FILM-COATED TABLET 10MG

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

INVAROX 10 MG
1 film-coated tablet contains 10 mg rivaroxaban.
Each 10mg film-coated tablet contains 29.00mg lactose per tablet.

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

3. PHARMACEUTICAL FORM

Light red, round biconvex tablets debossed with "10" on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Indications

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

INVAROX 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 'Special warnings and precautions for use*' for haemodynamically unstable PE patients).

4.2 Dosage and method of administration

Prevention of VTE in patients undergoing total hip replacement or total knee replacement surgery
The recommended dose is 10 mg rivaroxaban taken orally once daily. The initial dose should be taken within 6 to 10 hours after surgery, provided that haemostasis has been established.

The duration of treatment depends on the individual risk of the patient for venous thromboembolism which is determined by the type of orthopaedic surgery.

- For patients undergoing major hip surgery, a treatment duration of 5 weeks is recommended.
- For patients undergoing major knee surgery, a treatment duration of 2 weeks is recommended.

If a dose is missed the patient should take the 10mg INVAROX dose immediately and then continue on the following day with the once daily intake as before.

Treatment of DVT, treatment of PE and prevention of recurrent DVT and PE
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 INVAROX 10 mg once daily, a dose of INVAROX 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 'Special warnings and precautions for use'*).

	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 INVAROX immediately to ensure intake of 30 mg INVAROX 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 INVAROX 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.

Intake of INVAROX in relation to food
INVAROX may be taken with or without food.

For patients who are unable to swallow whole tablets, INVAROX tablet may be crushed and mixed with water or soft foods such as applesauce immediately prior to use and administered orally.
The crushed INVAROX tablet may be given through gastric tubes. Gastric placement of the tube should be confirmed before administering INVAROX. The crushed tablet should be administered in a small amount of water via a gastric tube after which it should be flushed with water (*see section 'Pharmacokinetic properties'*).

Additional information on special populations

Children and adolescents
Safety and efficacy have not been established in children and adolescents below 18 years.
INVAROX is not recommended for use in children or adolescents below 18 years of age due to a lack of data on safety and efficacy.

Geriatric patients
No dose adjustment is required based on age.

Gender
No dose adjustment is required based on gender.

Body weight
No dose adjustment is required based on body weight.

Patients with hepatic impairment
INVAROX is contraindicated in patients with hepatic disease which is associated with coagulopathy leading to a clinically relevant bleeding risk (*see sections 'Contraindications' and 'Pharmacokinetic*

properties'). INVAROX may be used with caution in cirrhotic patients with moderate hepatic impairment (Child Pugh B) if it is not associated with coagulopathy (*see sections 'Special warnings and precautions for use' and 'Pharmacokinetic properties'*).
No dose adjustment is necessary in patients with other hepatic diseases.

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

- For the prevention of VTE in adult patients undergoing elective hip or knee replacement surgery, no dose adjustment is necessary in patients with mild renal impairment (creatinine clearance 50 - 80 ml/min) or moderate renal impairment (creatinine clearance 30 - 49 ml/min) (*see section 'Pharmacokinetic properties'*).

- For the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE, no dose adjustment from the recommended dose is necessary in patients with mild renal impairment (creatinine clearance 50 - 80 ml/min) (*see section 'Pharmacokinetic properties'*).
  In patients with moderate (creatinine clearance 30 - 49 ml/min) or severe (creatinine clearance 15 - 29 ml/min) renal impairment: 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 'Special warnings and precautions for use', 'Pharmacodynamic properties' and 'Pharmacokinetic properties'*).
  When the recommended dose is 10 mg once daily, no dose adjustment from the recommended dose is necessary.

Converting from Vitamin K Antagonist (VKA) to INVAROX
For patients treated for DVT, PE and prevention of recurrence, VKA treatment should be stopped and INVAROX therapy should be initiated once the INR is ≤2.5.

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

Converting from INVAROX to Vitamin K antagonists (VKA)

There is a potential for inadequate anticoagulation during the transition from INVAROX to VKA. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that INVAROX can contribute to an elevated INR.

In patients converting from INVAROX 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 INVAROX and VKA, the INR should not be tested earlier than 24 hours (after the previous dose but prior to the next dose of INVAROX. Once INVAROX is discontinued INR testing may be done reliably 24 hours after the last dose *(see section 'Interaction with other medicinal products and other forms of interaction'*).

Converting from parenteral anti-coagulants to INVAROX

For patients currently receiving a parenteral anticoagulant, start INVAROX 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 INVAROX to parenteral anti-coagulants

Discontinue INVAROX and give the first dose of parenteral anticoagulant at the time that the next INVAROX dose would be taken.

4.3 Contraindications

Hypersensitivity to rivaroxaban or any excipient of the tablet.

Clinically significant active bleeding (e.g., intracranial bleeding, gastrointestinal bleeding).

Hepatic disease which is associated with coagulopathy leading to a clinically relevant bleeding risk (*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 'Interaction with other medicinal products and other forms of interaction'*).

4.4 Special warnings and precautions for use

Patients with prosthetic heart valves
INVAROX is not recommended for thromboprophylaxis in patients having recently undergone transcatheter aortic valve replacement (TAVR) based on data from a randomized controlled clinical study comparing a 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 INVAROX provides adequate anticoagulation in those patient populations.

Patients with high risk triple positive antiphospholipid syndrome
INVAROX 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)

Haemorrhagic risk
As with other anticoagulants, patients taking INVAROX are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. INVAROX 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. In patients receiving INVAROX for VTE prevention following total hip replacement or total knee replacement

sugery, this may be done by regular physical examination of the patients, close observation of the surgical wound drainage and periodic measurements of haemoglobin.
Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

Although treatment with rivaroxaban does not require routine monitoring of 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 sections 'Pharmacodynamic properties' and 'Pharmacokinetic properties'*).

Concomitant medication
INVAROX is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (e.g. ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir). These drugs are strong inhibitors of both CYP3A4 and P-gp. Therefore, these drugs may increase rivaroxaban plasma concentrations to a clinically relevant degree (2.6 fold on average) which may lead to an increased bleeding risk (*see section 'Interaction with other medicinal products and other forms of interaction'*).
The Azole anti-mycotic fluconazole a moderate CYP3A4 inhibitor, has however less effect on rivaroxaban exposure and can be co-administered with caution.

Hepatic impairment
In cirrhotic patients with moderate hepatic impairment (classified as Child Pugh B), rivaroxaban plasma levels may be significantly increased which may lead to an increased bleeding risk. INVAROX is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk. INVAROX may be used with caution in cirrhotic patients with moderate hepatic impairment (Child Pugh B) if it is not associated with coagulopathy (*see sections 'Dosage and method of administration', 'Contraindications' and 'Pharmacokinetic properties'*).

Renal impairment
INVAROX is to be used with caution in patients with moderate renal impairment (CrC: < 30-49 mL/min) receiving co-medications leading to increased rivaroxaban plasma concentrations (*see section 'Interaction with other medicinal products and other forms of interaction'*).
In patients with severe renal impairment (CrC: < 30 mL/min) rivaroxaban plasma levels may be significantly elevated (1.6- fold on average) which may lead to an increased bleeding risk. Due to limited clinical data, INVAROX should be used with caution in patients with CrC 15 - 29 mL/min.
No clinical data are available for patients with severe renal impairment (CrC: < 15 mL/min). Therefore use of INVAROX is not recommended in these patients.
Patients with severe renal impairment or increased bleeding risk and patients receiving concomitant systemic treatment with azole-antimycotics or HIV protease inhibitors are to be carefully monitored for signs of bleeding complications after initiation of treatment. This may be done by regular physical examination of the patients, close observation of the surgical wound drainage and periodic measurements of haemoglobin.

Hip fracture surgery
Rivaroxaban has not been studied in interventional clinical trials in patients undergoing hip fracture surgery. Limited clinical data from a non-interventional study are available for patients undergoing fracture related surgery of the lower limbs such as hip fracture surgery.

Haemodynamically unstable PE patients or patients who require thrombolysis or pulmonary embolectomy
INVAROX 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.

Bleeding risk
INVAROX, like other antithrombotics, should 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.

Care should be taken if patients are treated concomitantly with drugs affecting haemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet aggregation inhibitors, other antithrombotics, or selective serotonin reuptake inhibitors (SSRI), and serotonin norepinephrine reuptake inhibitors (SNRIs), (*see section 'Interaction with other medicinal products and other forms of interaction'*).

For patients at risk of gastrointestinal disease an appropriate prophylactic treatment may be considered.

Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

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 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 (e.g. 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 thromboprophylaxis.

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 (*see section 'Pharmacokinetic Properties'*).

An epidural catheter should not be withdrawn earlier than 18 hours after the last administration of INVAROX. INVAROX should be administered at earliest 6 hours after the removal of the catheter. If traumatic puncture occurs the administration of INVAROX should be delayed for 24 hours.

Surgery and interventions
If an invasive procedure or surgical intervention is required, INVAROX 10mg should be stopped at least 24 hours before the intervention, if possible and based on clinical judgement of the physician.

If the procedure cannot be delayed, the increased risk of bleeding should be assessed against the urgency of the intervention.

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

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

Information about excipients
Since this medicinal product contains lactose, patients with rare hereditary problems of lactose or galactose intolerance (e.g. the Lapp lactase deficiency or glucose-galactose malabsorption) should not take INVAROX.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions
Rivaroxaban does not inhibit CYP 3A4 or any other major CYP isoforms. Rivaroxaban does not induce CYP 3A4 or any other major CYP isoforms.

CYP3A4 and P-gp inhibitors
The concomitant use of INVAROX with strong CYP 3A4 and P-gp inhibitors, may lead to both reduced hepatic and renal clearance and thus significantly increased systemic exposure.
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 INVAROX 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 'Special warnings and precautions for use'*). Fluconazole is expected to have less effect on rivaroxaban exposure and can be co-administered with caution.

Other 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 twice daily), considered as strong CYP3A4 inhibitor and moderate P-gp inhibitor, led to a 1.5 fold increase in mean rivaroxaban AUC and a 1.4 fold increase in C_{max}. This increase is not considered clinically relevant.

Erythromycin (500 mg three times daily), 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 Cmax 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 Cmax when compared to subjects with normal renal function without co-medication (*see section 'Special warnings and precautions for use'*).

Fluconazole (400 mg once daily), considered as moderate CYP 3A4 inhibitor, led to a 1.4 fold increase in mean rivaroxaban AUC and a 1.3 fold increase in mean Cmax. This increase is considered as clinically not relevant.

CYP3A4 inducers
Co-administration of INVAROX with the strong CYP3A4 and P-gp inducer rifampicin led to an approximate 50 % decrease in mean rivaroxaban AUC, with parallel decreases in its pharmacodynamic effects. The concomitant use of INVAROX with other strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbitone or St. John's Wort) may also lead to a decreased rivaroxaban plasma concentration. Strong CYP3A4 inducers should be co-administered with caution. -

Pharmacodynamic interactions
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 'Special warnings and precautions for use'*).

NSAIDs/platelet aggregation inhibitors
No clinically relevant prolongation of bleeding time was observed after concomitant administration of rivaroxaban and 500 mg naproxen. Nevertheless, there may be individuals with a more pronounced pharmacodynamic response.
No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with 500 mg acetylsalicylic acid.
Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) did not show a pharmacokinetic interaction but a relevant increase in bleeding times 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 'Special warnings and precautions for use'*).

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.

Food and dairy products
10 mg INVAROX can be taken with or without food (*see section 'Dosage and method of administration'*).

Interactions shown not to exist
No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with midazolam (substrate of CYP3A4), digoxin (substrate of P-gp) or atorvastatin (substrate of CYP3A4 and P-gp).

Interactions with laboratory parameters
Clotting parameter tests (PT, aPTT, Hep Test®) are affected as expected by the mode of action of INVAROX (*see section 'Pharmacodynamic properties'*).

4.6 Pregnancy and lactation

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, INVAROX is contraindicated during pregnancy (*see section 'Contraindications'*).
Women of child-bearing potential should avoid becoming pregnant during treatment with INVAROX.

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

4.7 Effects on ability to drive and use machines

No studies of the effects on the ability to drive and use machines have been performed.
Syncope and dizziness have been reported in the post-operative setting and may affect the ability to drive and use machines, these adverse reactions have been reported to be uncommon (*see section 'Undesirable effects'*). Patients experiencing these adverse reactions should not drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

The safety of rivaroxaban has been evaluated in thirteen phase III studies including 53,103 patients exposed to rivaroxaban (see Table 1).

Table 1: Number of patients studied, total daily dose and maximum treatment duration in the rivaroxaban phase III studies

Indication	Number of patients*	Maximum daily dose	Maximum treatment duration
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	6,097	10 mg	39 days
Prevention of venous thromboembolism in medically ill patients	3,997	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
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	7,750	20 mg	41 months
Prevention of cardiovascular events in patients after an ACS	10,225	5 mg or 10 mg respectively, co-administered with either 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 2: Bleeding and anemia events rates in patients exposed to rivaroxaban across the completed 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
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.

Due to the pharmacological mode of action, rivaroxaban may be associated with an increased risk of occult or overt bleeding from any tissue and organ which may result in post hemorrhagic anemia. The risk of bleedings may be increased in certain patient groups e.g. patients with uncontrolled severe arterial hypertension and/or on concomitant medication affecting hemostasis (*see section 'Warnings and Precautions for Use'*). The signs, symptoms, and severity (including fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anemia (*see section 'Overdose/Management of bleeding'*).

Hemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnea, and unexplained shock. In some cases as a consequence of anemia, symptoms of cardiac ischemia 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 a hemorrhage should be considered in evaluating the condition in any anticoagulated patient.

Tabulated list of adverse reactions

The frequencies of ADRs reported with rivaroxaban are summarized in the table below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as:
very common (≥ 1/10), common (≥ 1/100 to < 1/10),
uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000),

Table 3: All treatment-emergent adverse drug reactions reported in patients in phase III studies (pooled RECORD 1-4, ROCKET, J-ROCKET, MAGELLAN, ATLAS and EINSTEIN (DVT/PE/Extension/CHOICE), and COMPASS*)

System Organ Class (MedDRA)	Common	Uncommon	Rare
Blood and the lymphatic system disorders	Anemia (incl. respective laboratory parameters)	Thrombocytosis (incl. platelet count increased) [A]	
Cardiac disorders		Tachycardia	
Eye disorders	Eye hemorrhage (incl. conjunctival hemorrhage)		
Gastrointestinal disorders	Gingival bleeding Gastrointestinal tract hemorrhage (incl. rectal hemorrhage) Gastrointestinal and abdominal pains Dyspepsia Nausea Constipation [A] Diarrhea Vomiting [A]	Dry mouth	
General disorders and administration site conditions	Fever [A] Edema peripheral Decreased general strength and energy (incl. fatigue and asthenia)	Feeling unwell (incl. malaise)	Localized edema [A]
Hepato-biliary disorders		Hepatic impairment	Jaundice
Immune system disorders		Allergic reaction Dermatitis allergic	
Injury, poisoning and postprocedural complications	Postprocedural hemorrhage (incl. postoperative anemia, and wound hemorrhage) Contusion	Wound secretion [A]	Vascular pseudoaneurysm[C]

Table 3: All treatment-emergent adverse drug reactions reported in patients in phase III studies (pooled RECORD 1-4, ROCKET, J-ROCKET, MAGELLAN, ATLAS and EINSTEIN (DVT/PE/Extension/CHOICE), and COMPASS*)

System Organ Class (MedDRA)	Common	Uncommon	Rare
Investigations	Increase in transaminases	Increase in bilirubin Increase in blood alkaline phosphatase [A] Increase in LDH [A] Increase in lipase [A] Increase in amylase [A] Increase in GGT [A]	Bilirubin conjugated increased (with or without concomitant increase of ALT)
Musculoskeletal, connective tissue and bone disorders	Pain in extremity [A]	Hemarthrosis	Muscle hemorrhage
Nervous system disorders	Dizziness Headache	Cerebral and intracranial hemorrhage Syncope	
Renal and urinary disorders	Urogenital tract hemorrhage (incl. hematuria and menorrhagia [B]) Renal impairment (incl. blood creatinine increased, blood urea increased) [A]		
Respiratory tract disorders	Epistaxis Hemoptysis		
Skin and subcutaneous tissue disorders	Pruritus (incl. uncommon cases of generalized pruritus) Rash Ecchymosis Cutaneous and subcutaneous hemorrhage	Urticaria	

Table 3: All treatment-emergent adverse drug reactions reported in patients in phase III studies (pooled RECORD 1-4, ROCKET, J-ROCKET, MAGELLAN, ATLAS and EINSTEIN (DVT/PE/Extension/CHOICE), and COMPASS*)

System Organ Class (MedDRA)	Common	Uncommon	Rare
Vascular disorders	Hypotension Hematoma		

[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 of recurrence as very common in women <55 years

[C] observed as uncommon in prevention of cardiovascular deaths in patients after an ACS (following percutaneous intervention)

* A pre-specified selective approach to adverse event collection was applied. As incidence of ADRs did not increase and no new ADR was identified, COMPASS study data were not included for frequency calculation in this table.

< ADR term representation is based on MedDRA version 20.0 >

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)).

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

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

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome

4.9 Overdose

Rare cases of overdose up to 600 mg have been reported without bleeding complications or other adverse reactions. Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg or above.
A specific antidote antagonizing the pharmacodynamic effect of rivaroxaban is not available. The use of activated charcoal to reduce absorption in case of INVAROX overdose may be considered. Due to the high plasma protein binding rivaroxaban is not expected to be dialyzable.

Management of Bleeding
Should a bleeding complication arise in a patient receiving rivaroxaban, the next administration should be delayed or treatment should be discontinued as appropriate. Rivaroxaban has a half-life of approximately 5 to 13 hours. Management should be individualized according to the severity and location of the

hemorrhage. Appropriate symptomatic treatment could be used as needed, such as mechanical compression (e.g., for severe epistaxis), surgical hemostasis with bleeding control procedures, fluid replacement and hemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anemia 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 individuals receiving rivaroxaban (*see section 'Pharmacodynamic properties'*). 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 individuals receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with the systemic hemostatics desmopressin in individuals receiving INVAROX.

5. PHARMACOLOGICAL PROPERTIES

5.1 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 patients undergoing major orthopedic surgery, the 5/95 percentiles for PT (Neoplastin) 2 - 4 hours after tablet intake (i.e. at the time of maximum effect) ranged from 13 to 25 sec.

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'*).

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 INVAROX. However, if clinically indicated, rivaroxaban concentrations can be measured by calibrated quantitative anti-Factor Xa tests (*see section 'Pharmacokinetic properties'*).

Clinical efficacy and safety
Prevention of VTE in patients undergoing total hip replacement or total knee replacement surgery The rivaroxaban clinical programme was designed to demonstrate the efficacy of rivaroxaban for the prevention of venous thromboembolic events (VTE), i.e. proximal and distal deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing major orthopaedic surgery of the lower limbs. Over 9,500 patients (7,050 in total hip replacement surgery and 2,531 in total knee replacement surgery) were studied in controlled randomised double-blind phase III clinical studies, the RECORD-programme.

Rivaroxaban 10 mg once daily started not earlier than 6 hours post-operatively was compared with enoxaparin 40 mg once daily started 12 hours pre-operatively.
In three phase III studies (see table 4), rivaroxaban significantly reduced the rate of total VTE (any venographically detected or symptomatic DVT, non-fatal PE and death) and major VTE (proximal DVT, non-fatal PE and VTE-related death), the pre-specified primary and major secondary efficacy endpoints. Furthermore, in all three studies the rate of symptomatic VTE (symptomatic DVT, non- fatal PE, VTE-related death) was lower in rivaroxaban treated patients compared to patients treated with enoxaparin.
The main safety endpoint, major bleeding, showed comparable rates for patients treated with rivaroxaban 10 mg compared to enoxaparin 40 mg.

Table 4: Efficacy and safety results from phase III clinical studies

	RECORD 1			RECORD 2			RECORD 3		
Study Population	4,541 patients undergoing total hip replacement surgery			2,509 patients undergoing total hip replacement surgery			2,531 patients undergoing total knee replacement surgery		
Treatment Dosage and Duration	Rivaroxaban 10 mg od 35 ± 4 days	Enoxaparin 40 mg od 35 ± 4 days	p	Rivaroxaban 10 mg od 35 ± 4 days	Enoxaparin 40 mg od 12 ± 2 days	p	Rivaroxaban 10 mg od 12 ± 2 days	Enoxaparin 40 mg od 12 ± 2 days	p
Total VTE	18 (1.1 %)	58 (3.7 %)	< 0.001	17 (2.0 %)	81 (9.3 %)	< 0.001	79 (9.6 %)	166 (18.9 %)	< 0.001
Major VTE	4 (0.2 %)	33 (2.0 %)	< 0.001	6 (0.6 %)	49 (5.1 %)	< 0.001	9 (1.0 %)	24 (2.6 %)	0.01
Sympto-matic VTE	6 (0.4 %)	11 (0.7 %)		3 (0.4 %)	15 (1.7 %)		8 (1.0 %)	24 (2.7 %)	
Major bleedings	6 (0.3 %)	2 (0.1 %)		1 (0.1 %)	1 (0.1 %)		7 (0.6 %)	6 (0.5 %)	

The analysis of the pooled results of the phase III trials corroborated the data obtained in the individual studies regarding reduction of total VTE, major VTE and symptomatic VTE with rivaroxaban 10 mg once daily compared to enoxaparin 40 mg once daily.

In addition to the phase III RECORD program, a post-authorization, non-interventional, open-label cohort study (XAMOS) has been conducted in 17,413 patients undergoing major orthopedic surgery of the hip or knee, to compare rivaroxaban with other standard-of-care pharmacological thromboprophylaxis in real-life setting. Symptomatic VTE occurred in 57 (0.6%) patients in the rivaroxaban group (n=8,778) and 88 (1.0%) of patients in the standard-of-care group (n=8,635; HR 0.63; 95% CI 0.43-0.91); safety population). Major bleeding occurred in 35 (0.4%) and 29 (0.3%) of patients in the rivaroxaban and standard-of-care groups (HR 1.10; 95% CI 0.67-1.80). Thus, the results were consistent with the results of the pivotal randomized studies.

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 12,800 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 5) 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 5: 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 6) 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 6: 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 7).

Table 7: 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 8) 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 8: 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 8).

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 8: 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–

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.

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 20mg (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.

5.2 Pharmacokinetic properties

Absorption and Bioavailability
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. INVAROX 10 mg tablets can be taken with or without food. Rivaroxaban pharmacokinetics are approximately linear up to about 15 mg once daily. At higher doses rivaroxaban displays dissolution limited absorption with decreased bioavailability and decreased absorption rate with increased dose. This is more marked in fasting state than in fed state. Variability in rivaroxaban pharmacokinetics is moderate with inter-individual variability (CV %) ranging from 30 % to 40 %, apart from the day of surgery and the following day when variability in exposure is high (70 %).

Absorption of rivaroxaban is dependent on the site of drug release in the GI tract. A 29% and 56% decrease in AUC and Cmax 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 Cmax 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 mean AUC was comparable to that after the whole tablet, and Cmax 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.

Distribution
Plasma protein binding in humans 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.

Metabolism and Elimination
Of the administered rivaroxaban dose, approximately 2/3 undergoes metabolic degradation, with half then 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 of a 10 mg dose the elimination becomes absorption rate limited with mean terminal half-lives of 7 to 11 hours.

Special populations 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.

Gender
There were no clinically relevant differences in pharmacokinetics and pharmacodynamics between male and female patients.

Body weight
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.

Children and adolescents
Safety and efficacy have not been established for children and adolescents below 18 years.

Ethnic differences
No clinically relevant inter-ethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding rivaroxaban pharmacokinetics and pharmacodynamics.

Hepatic impairment
INVAROX is contraindicated in patients with hepatic disease which is associated with coagulopathy leading to a clinically relevant bleeding risk.
Cirrhotic 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. No relevant difference in pharmacodynamic properties was observed between these groups.
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, due to significantly impaired drug clearance which indicates significant liver disease. 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.
INVAROX may be used with caution in cirrhotic patients with moderate hepatic impairment (Child Pugh B) if it is not associated with coagulopathy (*see sections 'Contraindications' and 'Special warnings and precautions for use'*).

Renal impairment
There was an increase in rivaroxaban exposure being inversely correlated to the decrease in renal function, as assessed via creatinine clearance measurements.
In individuals with mild (CrC: 50 - 80 mL/min), moderate (CrC: 30 - 49 mL/min) or severe (CrC: 15 - 29 mL/min) renal impairment, rivaroxaban plasma concentrations (AUC) were 1.4, 1.5 and 1.6-fold increased respectively as compared to healthy volunteers.
Corresponding increases in pharmacodynamic effects were more pronounced.
In individuals with mild, moderate or 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 CrC < 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. INVAROX is to be used with caution in patients with severe renal impairment creatinine clearance 15 - 29 mL/min (*see section 'Special warnings and precautions for use'*).

Concomitant administration of strong CYP 3A4 inducers
In a phase I trial, co-administration of rivaroxaban with the strong CYP 3A4 and P-gp inducer rifampicin led to an approximate 50% decrease in mean rivaroxaban AUC, with parallel decreases in its pharmacodynamic effects (*see section 'Interaction with other medicinal products and other forms of interaction'*).
In a phase IIa trial, the PK/PD of an adapted rivaroxaban dosing regimen (30 mg twice daily in the first 3 weeks of treatment, followed by 20 mg twice daily) has been studied in 19 patients treated for DVT or PE and who concomitantly were medicated with a strong CYP 3A4 and P-gp inducer (rifampicin or phenytoin). The adapted dosing regimen in these patients led to a similar exposure and pharmacodynamics when compared to patients treated for DVT (15 mg twice daily in the first 3 weeks of treatment, followed by 20 mg once daily) without the concomitant administration of a strong CYP 3A4 inducer.

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 10 mg od results in a steady state C_{max} of about 125 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 sec and the slope was around 3 to 4 sec/(100 µg/L). The results of the PK/PD analyses in Phase II were consistent with the data established in healthy subjects. In patients, baseline factor Xa and PT were influenced by the surgery resulting in a difference in the concentration-PT slope between the day post-surgery and steady state.

In patients receiving rivaroxaban 10 mg once daily for prevention of VTE, 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 101 (7 - 273) and 14 (4 - 51) µg/l, respectively.

5.3 Preclinical safety data

In rats, increased IgG and IgA plasma levels were seen at clinically relevant exposure levels. 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Excipients
Sodium laurilsulfate
Lactose
Poloxamer 188
Cellulose, microcrystalline (E460)
Croscarmellose sodium
Magnesium stearate (E470b)
Silica, colloidal anhydrous (E551)

Film-coating
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol 3350 (E1521)
Red iron oxide (E172)
Water, purified

6.2 Incompatibilities

None known.

6.3 Storage Conditions

Do not store above 30°C

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Aluminium-PVC/PE/PVdC blisters of 28 tablets.

7. MANUFACTURER

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8. DATE OF REVISION OF THE TEXT

June 2023