1. NAME OF THE MEDICINE

IXAROLA 10 Film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Contains sugar: Each film-coated tablet contains 26.51 mg lactose (as monohydrate), see section 4.4.

For full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Film-coated tablets

Light red, round, biconvex, film-coated tablets, 6 mm in diameter, debossed with "Triangle 10" on the top side and the BAYER-cross on the bottom side of the tablet.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

IXAROLA 10 film-coated tablets are indicated for the prevention of venous thromboembolism (VTE) in patients undergoing major orthopaedic surgery of the lower limbs.
Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults. (See section 4.4 for haemodynamically unstable PE patients.)

4.2 Posology and method of administration

The recommended dose is one IXAROLA 10 tablet once daily for the prevention of venous thromboembolism (VTE) in major orthopaedic surgery.

The initial dose should be taken within 6 - 10 hours after surgery provided that haemostasis has been established.
If a dose is missed the patient should take IXAROLA 10 immediately and continue on the following day with the once daily intake as before.

Duration of treatment
The duration of treatment depends on the type of major orthopaedic surgery.
After major hip surgery patients should be treated for 5 weeks.
After major knee surgery patients should be treated for 2 weeks.

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 IXAROLA 10 mg once daily, a dose of IXAROLA 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 4.4).

	Time period	**Dosing schedule**	**Total 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

If a dose is missed during the 15 mg twice daily treatment phase (day 1 - 21), the patient should take IXAROLA immediately to ensure intake of 30 mg IXAROLA 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 IXAROLA 10 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.

Converting from Vitamin K Antagonists (VKA) to IXAROLA10
For patients treated for DVT, PE and prevention of recurrence, VKA treatment should be stopped and IXAROLA 10 therapy should be initiated once the INR is ≤ 2.5.

When converting patients from VKAs to IXAROLA 10, International Normalised Ratio (INR) values will be falsely elevated after the intake of IXAROLA 10. The INR is not valid to measure the anticoagulant activity of IXAROLA 10, and therefore should not be used (see section 4.5).

Converting from IXAROLA 10 to Vitamin K antagonists (VKA)

There is a potential for inadequate anticoagulation during the transition from IXAROLA 10 to VKA. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that IXAROLA 10 can contribute to an elevated INR.

In patients converting from IXAROLA 10 to VKA, VKA should be given concurrently until the INR is ≥ 2.0. For the first two days of the conversion period, standard initial dosing of VKA should be used followed by VKA dosing, as guided by INR testing. While patients are on both IXAROLA 10 and VKA the INR should not be tested earlier than 24 hours after the previous dose but prior to the next dose of IXAROLA 10. Once IXAROLA is discontinued INR testing may be done reliably at least 24 hours after the last dose (see sections 4.5 and 5.2).

Converting from parenteral anticoagulants to IXAROLA 10

For patients currently receiving a parenteral anticoagulant, discontinue the parenteral anticoagulant and start IXAROLA 10, 0 to 2 hours before the time that the next scheduled administration of the parenteral medicinal product (e.g. low molecular weight heparins) would be due or at the time of discontinuation of a continuously administered parenteral medicinal product (e.g. intravenous unfractionated heparin).

Converting from IXAROLA 10 to parenteral anticoagulants

Give the first dose of parenteral anticoagulant at the time the next IXAROLA 10 dose would be taken.

Special patient populations
Elderly (above 65 years), Gender and Body Weight:
No dose adjustment is required for these patient populations.

Paediatric population
Children (up to 18 years of age)
The safety and efficacy of IXAROLA 10 has not been established in children. No clinical data is available for children.

Patients with impaired liver function
IXAROLA 10 is contra-indicated in patients with significant hepatic disease which is associated with coagulopathy leading to a clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C. (see section 4.3 and 5.2).

No dose adjustment is necessary in patients with other hepatic diseases.

Limited clinical data in patients with moderate hepatic impairment indicate a significant increase in the pharmacological activity. No clinical data are available for patients with severe hepatic impairment.

Patients with impaired renal function
For the prevention of VTE in adult patients undergoing elective hip or knee replacement surgery, no dose adjustment is required if IXAROLA 10 is administered in patients with mild (creatinine clearance 50 – 80 mL/min) or moderate (creatinine clearance < 30 - 50 mL/min) renal impairment.

Limited clinical data for patients with severe renal impairment (creatinine clearance < 30 mL/min) indicate that rivaroxaban plasma levels are significantly increased in this patient population. Therefore IXAROLA 10 must be used with caution in these patients (see section 4.4). Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.4 and 5.2).

- 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 5.2).
  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 4.4, 5.1 and 5.2).

  When the recommended dose is 10 mg once daily, no dose adjustment from the recommended dose is necessary.

Method of administration

IXAROLA 10 is for oral use.

The tablets can be taken with or without food (see sections 4.5 and 5.2).

For patients who are unable to swallow whole tablets, IXAROLA 10 tablet may be crushed and mixed with water or apple puree immediately prior to use and administered orally.

The crushed IXAROLA 10 tablet may also be given through gastric tubes after confirmation of the correct gastric placement of the tube. 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 5.2).

4.3 Contraindications

IXAROLA 10 is contra-indicated in patients with:

- 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 including cirrhotic patients with Child Pugh B and C (see section 5.2).

- Lesion or condition, if considered to be a significant risk for 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 anticoagulants, e.g. unfractionated heparin (UFH), low molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, dabigatran etexilate, apixaban, etc.) except under specific circumstances of switching anticoagulant therapy (see section 4.2) or when UFH is given at doses necessary to maintain an open central venous or arterial catheter (see section 4.5).

- Pregnancy and lactation (see section 4.6).
- Treatment with rivaroxaban in patients with persistent triple positive antiphospholipid syndrome (APS) is contraindicated.

4.4 Special warnings and precautions for use

IXAROLA 10 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
- Recent gastrointestinal ulcerations
- Vascular retinopathy
- Recent intracranial or intracerebral haemorrhage
- Shortly after brain, spinal or ophthalmological surgery
- other gastrointestinal disease without active ulceration that can potentially lead to bleeding complications (e.g. inflammatory bowel disease, oesophagitis, gastritis and gastroesophageal reflux disease)
- bronchiectasis or history of pulmonary bleeding

Haemorrhagic risk

As with other anticoagulants, patients taking IXAROLA 10 are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. IXAROLA 10 administration should be discontinued if severe haemorrhage occurs (see section 4.9).

In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary including abnormal vaginal or increased menstrual bleeding) and anaemia 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 and quantify the clinical relevance of overt bleeding, as judged to be appropriate. Any unexplained fall in haemoglobin or blood pressure should lead to a search for a bleeding site.

Several sub-groups of patients, as detailed above, are at increased risk of bleeding. These patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment (see section 4.8). In patients receiving IXAROLA 10 for VTE prevention following elective hip or knee replacement surgery, this may be done by regular physical examination of the patients, close observation of the surgical wound drainage and periodic measurements of haemoglobin.

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 5.1 and 5.2).

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.

Renal impairment
In 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. IXAROLA 10 is to be used with caution in patients with creatinine clearance 15 - 29 ml/min. Use is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.2 and 5.2). In patients with moderate renal impairment (creatinine clearance 30 - 49 ml/min) concomitantly receiving other medicinal products which increase rivaroxaban plasma concentrations IXAROLA 10 is to be used with caution (see section 4.5).

Interaction with other medicinal products
IXAROLA 10 must be used with caution in patients receiving concomitant systemic treatment with azole-antimycotics (e.g. ketoconazole) or HIV protease inhibitors (e.g. ritonavir). These drugs are strong inhibitors of both CYP 3A4 and P-gp. Therefore, these drugs may increase rivaroxaban plasma concentrations to a clinically relevant degree (see section 4.5).

After treatment is initiated patients should be carefully monitored for signs of bleeding complications. This may be done by regular physical examination of the patients, close observation of the surgical wound drainage and periodic measurements of haemoglobin.

Care should be taken if patients are treated concomitantly with drugs affecting haemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid (ASA), platelet aggregation inhibitors, or selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs) or other antithrombotics. For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered (see section 4.5).

IXAROLA 10 should be used in women of childbearing potential only with effective contraception.
No QTc prolonging effect was observed with IXAROLA 10.

Patients with prosthetic valves

IXAROLA 10 should not be used for thromboprophylaxis in patients having recently undergone transcatheter aortic valve replacement (TAVR). Safety and efficacy of IXAROLA 10 have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that IXAROLA 10 provides adequate anticoagulation in this patient population. Treatment with IXAROLA 10 is not recommended for these patients.

Patients with antiphospholipid syndrome (APS)

Treatment of patients with established APS is not recommended as evidence regarding safety and efficacy, including the benefit/harm balance of rivaroxaban (and DOACs with the same mechanism of action) in APS patients, is inconclusive. There is some evidence that treatment of persistently triple positive APS patients with rivaroxaban is associated with an increased risk of recurrent arterial thrombotic events compared with treatment of these patients with warfarin; a vitamin K antagonist (see section 4.3).

Hip fracture surgery

IXAROLA 10 has not been studied in interventional clinical studies in patients undergoing hip fracture surgery to evaluate efficacy and safety.

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

IXAROLA 10 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 IXAROLA 10 have not been established in these clinical situations.

Spinal/epidural anaesthesia or puncture

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 increased by post-operative 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) anaesthesia 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 5.2).

An epidural catheter should not be withdrawn earlier than 18 hours after the last administration of IXAROLA 10.

IXAROLA 10 should be administered at earliest 6 hours after the removal of the catheter.

If traumatic puncture occurs the administration of IXAROLA 10 should be delayed for 24 hours.

Dosing recommendations before and after invasive procedures and surgical intervention other than elective hip or knee replacement surgery.

If an invasive procedure or surgical intervention is required, IXAROLA 10 mg should be stopped at least 24 hours before the intervention, if possible and based on the 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.

IXAROLA 10 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 as determined by the treating physician (see section 5.2).

Elderly population

Increasing age may increase haemorrhagic risk (see section 5.2).

Dermatological reactions

Serious skin reactions, including Stevens-Johnson syndrome/toxic epidermal necrolysis and DRESS syndrome, have been reported during post-marketing surveillance in association with the use of IXAROLA 10 (see section 4.8). Patients appear to be at highest risk for these reactions early in the course of therapy: the onset of the reaction occurring in the majority of cases within the first weeks of treatment. IXAROLA 10 should be discontinued at the first appearance of a severe skin rash (e.g. spreading, intense and/or blistering), or any other sign of hypersensitivity in conjunction with mucosal lesions.

Information about excipients

Since IXAROLA 10 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 IXAROLA 10. IXAROLA 10 tablets contain less than 1 mmol sodium (23 mg) per dose, that is to say essentially "sodium free".

4.5 Interactions with other medicines and other forms of interactions

Pharmacokinetic interactions

Rivaroxaban is cleared mainly via cytochrome P450-mediated (CYP 3A4, CYP 2J2) hepatic metabolism and renal excretion of the unchanged drug, involving the P-glycoprotein (P gp) / breast cancer resistance protein (Bcrp) transporter systems (see Pharmacokinetics).

CYP Inhibition

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

CYP Induction

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

Effects on IXAROLA 10

The concomitant use of IXAROLA 10 with strong CYP 3A4 and P gp inhibitors, may lead to both reduced hepatic and renal clearance and thus significantly increased systemic exposure.

CYP3A4 and P-gp inhibitors

Co-administration of IXAROLA 10 with the azole-antimycotic ketoconazole (400 mg once daily) a strong CYP 3A4 and P gp inhibitor, led to a 2.6-fold increase in mean rivaroxaban steady state AUC and a 1.7 fold increase in mean rivaroxaban Cmax, with significant increases in its pharmacodynamic effects which may lead to an increased bleeding risk. Therefore, the use of IXAROLA 10 is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics such as ketoconazole, itraconazole,

voriconazole and posaconazole or HIV protease inhibitors. These active substances are strong inhibitors of both CYP3A4 and P-gp (see section 4.4).

Co-administration of IXAROLA 10 with the HIV protease inhibitor ritonavir (600 mg twice daily), a strong CYP 3A4 and P gp inhibitor, led to a 2.5-fold increase in mean rivaroxaban AUC and a 1.6 fold increase in mean rivaroxaban Cmax, with significant increases in its pharmacodynamic effects. Therefore IXAROLA 10 must be used with caution in patients receiving concomitant systemic treatment with azole-antimycotics or HIV-protease inhibitors (see section 4.4).

Drugs strongly inhibiting only one of the rivaroxaban elimination pathways, either CYP 3A4 or P gp, potentially increase rivaroxaban plasma concentrations. The expected increase is considered as clinically not relevant.

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 a day), 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}. The interaction with clarithromycin is likely not clinically relevant in most patients but can be potentially significant in high-risk patients. (For patients with renal impairment: see section 4.4).

Erythromycin (500 mg three times daily), which inhibits CYP 3A4 and P gp moderately, led to a 1.3-fold increase in mean rivaroxaban steady state AUC and Cmax. This increase is within the magnitude of the normal variability of AUC and Cmax and is considered as clinically not relevant but can be potentially significant in high-risk patients. 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 CR_{max} when compared to subjects with normal renal function. In subjects with moderate renal impairment, erythromycin led to a 2.0 fold increase in mean rivaroxaban AUC and 1.6-fold increase in CR_{max} when compared to subjects with normal renal function. The effect of erythromycin is additive to that of renal impairment (see section 4.4).

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 Cmax. The interaction with fluconazole is likely not clinically relevant in most patients but can be potentially significant in high-risk patients. (For patients with renal impairment: see section 4.4).

Given the limited clinical data available with dronedarone, co-administration with rivaroxaban should be avoided.

Pharmacodynamic interactions
Anticoagulants

After combined administration of enoxaparin (40 mg single dose) with IXAROLA 10 (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 ~~(see section 4.4)~~. Due to the increased bleeding risk care is to be taken if patients are treated concomitantly with any other anticoagulants (see sections 4.3 and 4.4).

NSAIDs/platelet aggregation inhibitors
No clinically relevant prolongation of bleeding time was observed after concomitant administration of IXAROLA 10 and 500 mg naproxen. Nevertheless there may be individuals with more pronounced pharmacodynamic response (see section 4.4).

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 (see section 4.4).
Care is to be taken if patients are treated concomitantly with NSAIDs (including acetylsalicylic acid) and platelet aggregation inhibitors because these medicinal products typically increase the bleeding risk (see section 4.4).

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 IXAROLA 10 clinical programme, 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 IXAROLA (20 mg) or from IXAROLA (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 *(Hypericum perforatum)*) may also lead to reduced rivaroxaban plasma concentrations. Therefore, concomitant administration of strong CYP3A4 inducers should be avoided unless the patient is closely observed for signs and symptoms of thrombosis.

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). IXAROLA 10 neither inhibits nor induces any major CYP isoforms like CYP3A4.

No clinically relevant interaction with food was observed (see section 4.2).

Interactions with laboratory parameters
Clotting parameter tests (PT, aPTT, HepTest®) are affected as expected by the mode of action of IXAROLA 10.

4.6 Fertility, pregnancy and lactation:
Pregnancy
No human data on the use of IXAROLA 10 in pregnant women are available.
Safety and efficacy of IXAROLA 10 have not been established in pregnant women.
In rats and rabbits IXAROLA 10 showed pronounced maternal toxicity with placental changes related to its pharmacological mode of action (e.g., haemorrhagic complications). No primary teratogenic potential was identified. Animal data show that rivaroxaban crosses the placental barrier. Therefore, use of IXAROLA 10 is contra-indicated throughout pregnancy.
IXAROLA 10 should be used in women of childbearing potential only with effective contraception.

Breast-feeding

No human data on use of IXAROLA 10 in nursing mothers are available.
Safety and efficacy of IXAROLA 10 have not been established in nursing mothers.
In rats rivaroxaban is secreted into breast milk. Therefore IXAROLA 10 may only be administered after breastfeeding is discontinued.
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 5.3).

4.7 Effect on ability to drive or use machines
IXAROLA has minor influence on the ability to drive and use machines. Adverse reactions like syncope (frequency: uncommon) and dizziness (frequency: common) have been reported (see section 4.8). 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 twenty phase III studies including 70,021 patients exposed to rivaroxaban (see Table 1).

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

Indication	Number of patients*	Total 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 VTE in medically ill patients	3,997	10 mg	39 days
Treatment of DVT, PE and prevention of recurrence	6,790	Day 1 - 21: 30 mg Day 22 and onwards: 20 mg After at least 6 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 atherothrombotic events in patients after an acute coronary syndrome (ACS)	10,225	5 mg or 10 mg respectively, co-administered with either ASA or ASA plus clopidogrel or ticlopidine	31 months
Prevention of atherothrombotic events in patients with CAD/PAD	18,244	5 mg co-administered with ASA or 10 mg alone	47 months
Prevention of stroke and prevention of systemic embolism in patients with a recent Embolic Stroke of Undetermined Source	3,562	15 mg od	24 months
Prevention of symptomatic VTE events and VTE-related deaths for a period of 45 days post-hospital discharge in high-risk medically ill	5,982	10 (or 7.5) mg od	45 days
Reducing the risk of death, myocardial infarction or stroke in subjects with heart failure and	2,499	2.5 mg bid combined with ASA 100 mg	42 months (or >1,260 days)

Indication	Number of patients*	Total daily dose	Maximum treatment duration
significant coronary artery disease following an episode of decompensated heart failure			
Reducing the cumulative incidence of DVT, PE, and VTE-related death in adult subjects with various cancer types at high risk of developing a VTE	405	10 mg od	6.9 months or (207 days)
Comparing a rivaroxaban-based antithrombotic strategy to an antiplatelet-based strategy after transcatheter aortic valve replacement (TAVR) to optimize clinical outcomes	801	10 mg od + low dose ASA / post 90d 10 mg alone	24 months (or 720 days)
Treatment of venous thromboembolism (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 and PE with 20 mg rivaroxaban once daily	12 months
Prevention of atherothrombotic events in patients after recent revascularization procedure of the lower limb due to symptomatic PAD	3,256	2.5 mg bid combined with ASA 100 mg	42 months

* Patients exposed to at least one dose of rivaroxaban

Table 2: Bleeding* and anaemia events rates in patients exposed to rivaroxaban across the completed phase III studies

Indication	Any bleeding	Anaemia
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 recurrence	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 atherothrombotic events in patients after an ACS	22 per 100 patient years	1.4 per 100 patient years
Prevention of atherothrombotic events in patients with CAD/PAD	6.7 per 100 patient years	0.15 per 100 patient years**
Prevention of stroke and prevention of systemic embolism in patients with a recent Embolic Stroke of Undetermined Source	12.4 % of patients	0.3 % of patients*
Prevention of symptomatic VTE events and VTE-related deaths for a period of 45 days post-hospital discharge in high –risk medically ill	3.0 % of patients	<0.1 % of patients*
Reducing the risk of death, myocardial infarction or stroke in subjects with heart failure and significant coronary artery disease following an episode of decompensated heart failure	11.5% of patients	1.4% of patients*

Reducing the cumulative incidence of DVT, PE, and VTE-related death in adult subjects with various cancer types at high risk of developing a VTE	23.2 of patients	14.1 % of patients*
Comparing a rivaroxaban-based antithrombotic strategy to an antiplatelet-based strategy after transcatheter aortic valve replacement (TAVR) to Optimize clinical outcomes	25.6 % of patients	2.4 % of patients*
Treatment of venous thromboembolism (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 atherothrombotic events in patients after recent revascularization procedure of the lower limb due to symptomatic	(16.9% of patients) 8.38 per 100 patient years	(1.5% of patients*) 0.74 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 IXAROLA are summarised in Table 3 below by system organ class (in MedDRA) and by frequency.
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); very rare (< 1/10,000); not known (cannot be estimated from the available data)

Table 3:
All adverse reactions reported in patients in phase III clinical trials or through post-marketing use*

Common **= 1 % to < 10 %**	**Uncommon** **= 0,1 % to < 1 %**	**Rare** **= 0,01 % to < 0,1 %**	**Very rare**	**Not known**
Blood and the lymphatic system disorders				
Anaemia (incl.	Thrombocythemia (incl.			

Table 3:
All adverse reactions reported in patients in phase III clinical trials or through post-marketing use*

Common **= 1 % to < 10 %**	**Uncommon** **= 0,1 % to < 1 %**	**Rare** **= 0,01 % to < 0,1 %**	**Very rare**	**Not known**
respective lab parameters)	platelet count increased)			
Immune system disorders				
	Allergic reaction, dermatitis allergic	~~Dermatitis, allergic~~		
Nervous system disorders				
Dizziness Headache	Cerebral and intracranial, Haemorrhage syncope (incl. loss of consciousness)			
Eye disorders				
Eye haemorrhage (incl. conjunctival haemorrhage)				
Cardiac disorders				
	Tachycardia			
Vascular disorders				
Hypotension, haematoma				
Respiratory, thoracic and mediastinal disorders				
Epistaxis, haemoptysis				
Gastrointestinal disorders				
Nausea Gingival bleeding, gastrointestinal tract haemorrhage (incl. rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, constipation[A], diarrhoea, vomiting[A]	Dry mouth			
Hepatobiliary disorders				
	Hepatic impairment,	Jaundice		
Skin and subcutaneous tissue disorders				
Pruritus (incl. uncommon cases			Stevens-Johnson	

Table 3:
All adverse reactions reported in patients in phase III clinical trials or through post-marketing use*

Common = 1 % to < 10 %	Uncommon = 0,1 % to < 1 %	Rare = 0,01 % to < 0,1 %	Very rare	Not known
of generalised pruritus), rash, ecchymosis, cutaneous and subcutaneous haemorrhage	Urticaria (incl. rare cases of generalised urticaria)		syndrome/ Toxic Epidermal Necrolysis, DRESS syndrome	
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)				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. fatigue, asthenia)	Localised oedema[A]		
Investigations				
Increase in transaminases	Increased LDH[A], increased lipase[A], increased amylase[A] Blood bilirubin increased Increased alkaline phosphatase Increase in GGT [A]	Bilirubin conjugated increased (with or without concomitant increase of ALT)		

Table 3: **All adverse reactions reported in patients in phase III clinical trials or through post-marketing use***				
Common **= 1 % to < 10 %**	**Uncommon** **= 0,1 % to < 1 %**	**Rare** **= 0,01 % to < 0,1 %**	**Very rare**	**Not known**
Injury, poisoning and procedural complications				
Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage), contusion,	Wound secretion[A]	Vascular pseudoaneurysm[C]		

[A] observed after major orthopedic surgery of the lower limbs
[B] observed in VTE treatment as very common in women <55 years
[C] observed as uncommon in prevention therapy in ACS (following percutaneous intervention)
* A pre-specified selective approach to adverse event collection was applied. The incidence of ADRs did not increase and no new ADR was identified from the analysis of the adult phase III study data.

Description of selected adverse reactions

Due to the pharmacological mode of action, IXAROLA 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 '* Special 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 IXAROLA. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

Post marketing observations

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

Immune system disorders: Angioedema and allergic oedema.
Hepatobiliary disorders: Cholestasis, Hepatitis (incl. hepatocellular injury).
Blood and lymphatic system disorders: Thrombocytopenia.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any

suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8

4.9 Overdosage

Overdose following administration of IXAROLA 10 may lead to haemorrhagic complications due to its pharmacodynamic properties.

Rare cases of overdose up to 1960 mg have been reported. In case of overdose, observe your patient carefully for bleeding complications or other adverse reactions (see section 'Management of bleeding'). 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.

A specific antidote antagonising the pharmacodynamic effect of rivaroxaban is not available in South Africa.

The use of activated charcoal to reduce absorption in case of IXAROLA 10 overdose may be considered. Administration of activated charcoal up to 8 hours after overdose may reduce the absorption of rivaroxaban.

Due to the high plasma protein binding IXAROLA 10 is not expected to be dialysable.

Management of bleeding

Should bleeding occur, management of the haemorrhage may include the following steps:

- Delay of next IXAROLA 10 administration or discontinuation of treatment as appropriate. Rivaroxaban has a half-life of approximately 5 to 13 hours. Management should be individualised according to the severity and location of the haemorrhage.
- Appropriate symptomatic treatment, e.g. mechanical compression (e.g., for severe epistaxis), surgical interventions, fluid replacement and haemodynamic support, blood product or component transfusion should be considered.

If bleeding cannot be controlled by the above measures, consider administration of one of the following procoagulants:

- Activated prothrombin complex concentrate (APCC)
- Prothrombin complex concentrate (PCC)
- Recombinant Factor VIIa (rF VIIa).

Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of IXAROLA 10. There is no scientific rationale for benefit or experience with systemic haemostatics (e.g. desmopressin, aprotinin, tranexamic acid, aminocaproic acid) in individuals receiving IXAROLA 10. There is neither scientific rationale for benefit nor experience with the use of the systemic haemostatic desmopressin in individuals receiving IXAROLA 10.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents, direct factor Xa inhibitors,

ATC code: B01AF01

Mechanism of action
Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability.

Activation of Factor X to Factor Xa (FXa) via the intrinsic and extrinsic pathway plays a central role in the cascade of blood coagulation. FXa directly converts prothrombin to thrombin through the prothrombinase complex, and ultimately, this reaction leads to fibrin clot formation and activation of platelets by thrombin. One molecule of FXa is able to generate more than 1000 molecules of thrombin due to the amplification nature of the coagulation cascade. In addition, the reaction rate of prothrombinase-bound FXa increases 300,000-fold compared to that of free FXa and causes an explosive burst of thrombin generation.

Selective inhibitors of FXa can terminate the amplified burst of thrombin generation. Consequently, several specific and global clotting tests are affected by rivaroxaban. Dose dependent inhibition of Factor Xa activity was observed in humans.

Pharmacodynamic effects
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 Normalised Ratio) is only calibrated and validated for coumarins and cannot be used for any other anticoagulant. In patients undergoing major orthopaedic surgery, the 5/95 percentiles for PT, 2 - 4 hours after tablet intake (i.e. at the time of maximum effect), ranged from 13 to 25 seconds.

The activated partial thomboplastin time (aPTT) and HepTest® are also prolonged dose-dependently; however, they are not recommended to assess the pharmacodynamics effect of rivaroxaban.

Anti-Factor Xa activity is also influenced by rivaroxaban; however no standard for calibration is available.

There is no need for monitoring of coagulation parameters during treatment with rivaroxaban.

Clinical efficacy and safety

Prevention of VTE in adult patients undergoing elective hip or knee replacement surgery
The rivaroxaban clinical programme was designed to demonstrate the efficacy of rivaroxaban for the prevention of 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 (od) started no sooner than 6 hours post-operatively was compared with enoxaparin 40 mg once daily started 12 hours pre-operatively.
In all 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 dose and duration after surgery	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
Symptomatic 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 studies 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 programme, a post-authorization, non-interventional, open-label cohort study (XAMOS) has been conducted in 17,413 patients undergoing major orthopaedic surgery of the hip or knee, to compare rivaroxaban with other pharmacological thromboprophylaxis (standard-of-care) under 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 randomised studies.

Treatment of DVT, PE and prevention of recurrent DVT and PE

The IXAROLA clinical programme was designed to demonstrate the efficacy of IXAROLA in the initial and continued treatment of acute DVT and PE and prevention of recurrence.

Over 12,800 patients were studied in four randomised 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. IXAROLA 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 randomisation date (median: 351 days). IXAROLA 20 mg once daily and IXAROLA 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.
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 (HR): 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 HR 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 HR 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 dose and duration	**IXAROLA[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 HR of 2.0); HR: 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); HR: 1.123 (0.749 – 1.684)). The prespecified net clinical benefit (primary efficacy outcome plus major bleeding events) was reported with a HR 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 HR 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) were 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 HR 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 dose and duration	**IXAROLA[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 HR of 2.0); HR: 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 dose and duration	**IXAROLA[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 HR of 1.75); HR: 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 HR 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 dose and duration	**IXAROLA[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), HR: 0.185 (0.087 - 0.393)

In the Einstein Choice study (Table 9) IXAROLA 20 mg and 10 mg were both superior to 100 mg acetylsalicylic acid for the primary efficacy outcome. The principal safety outcome (major bleeding events) was similar for patients treated with IXAROLA 20 mg and 10 mg once daily compared to 100 mg acetylsalicylic acid.

Table 9: Efficacy and safety results from phase III Einstein Choice

Study population	**3,396 patients continued prevention of recurrent venous thromboembolism**		
Treatment dose	**IXAROLA 20 mg od N=1,107**	**IXAROLA 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%)
Symptomatic recurrent VTE, MI, stroke, or non-CNS systemic embolism	19 (1.7%)	18 (1.6%)	56 (5.0%)
Major bleeding events	6 (0.5%)	5 (0.4%)	3 (0.3%)
Clinically relevant non-major bleeding	30 (2.7)	22 (2.0)	20 (1.8)
Symptomatic recurrent VTE or major bleeding (net clinical benefit)	23 (2.1%)+	17 (1.5%)++	53 (4.7%)

* p<0.001(superiority) IXAROLA 20 mg od vs ASA 100 mg od; HR=0.34 (0.20–0.59)
** p<0.001 (superiority) IXAROLA 10 mg od vs ASA 100 mg od; HR=0.26 (0.14–0.47)
+ IXAROLA 20 mg od vs. ASA 100 mg od; HR=0.44 (0.27–0.71), p=0.0009 (nominal)
++ IXAROLA 10 mg od vs. ASA 100 mg od; HR=0.32 (0.18–0.55), p<0.0001 (nominal)

In addition to the phase III EINSTEIN programme, 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 in clinical practice. 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 analysis was used to adjust for measured baseline differences but residual confounding may, in spite of this, influence the results. Adjusted HRs comparing rivaroxaban and standard-of-care 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.

These results in clinical practice are consistent with the established safety profile in this indication.

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 enrolment of 120 patients due to an excess of events among patients in the rivaroxaban arm. Mean follow-up was 569 days. 59 patients were randomized to rivaroxaban 20 mg (15 mg for patients with creatinine clearance (CrCl) <50 mL/min) and 61 to warfarin (INR 2.0-3.0). Thromboembolic events occurred in 12 % of patients randomized to rivaroxaban (4 ischaemic strokes and 3 myocardial infarctions). 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
The absolute bioavailability of rivaroxaban is approximately 100 % for the 10 mg dose. Rivaroxaban is rapidly absorbed with maximum concentrations (C_{max}) appearing 2 - 4 hours after tablet intake.

Administration of rivaroxaban tablets with food (high-calorie / high-fat meal) showed no significant food effects. Rivaroxaban 10 mg dose can be taken with or without food. (see Dosage and Direction for Use).

Rivaroxaban pharmacokinetics is linear with no relevant undue accumulation beyond steady-state after multiple doses.

Variability in rivaroxaban pharmacokinetics is moderate with inter-individual variability (CV %) ranging from 30 % to 40 %.

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 L.

Metabolism and Elimination
Rivaroxaban is eliminated by metabolic degradation (approximately 2/3 of the administered dose) as well as by direct renal excretion of unchanged compound (approximately 1/3). Rivaroxaban is metabolised via CYP 3A4, CYP 2J2 and CYP-independent mechanisms. Oxidative degradation of the morpholinone moiety and hydrolysis of the amide bonds are the major sites of biotransformation.

Elimination of rivaroxaban and metabolites occurs via both renal and faecal routes.

Approximately 66 % of a rivaroxaban dose is eliminated via the kidneys, with 30 - 40 % excreted as unchanged drug in the urine via both glomerular filtration and active renal secretion. 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 low-clearance drug. Elimination of rivaroxaban from plasma occurred 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.

Special populations

Gender/Elderly (above 65 years)
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 (see Dosage and Directions for Use).

There were no clinically relevant differences in pharmacokinetics between male and female patients (see Dosage and Directions for Use).

Different weight categories
Extremes in body weight (< 50 kg versus > 120 kg) had only a small influence on rivaroxaban plasma concentrations (less than 25 %) (see Dosage and Directions for use).

Children (up to 18 years of age)
No data is available for this patient population (see Dosage and Directions for Use).

Inter-ethnic differences
No clinically relevant inter-ethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding pharmacokinetics and pharmacodynamics (see Dosage and Directions for Use).

Hepatic impairment
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. The inhibition of Factor Xa activity was increased by a factor of 2.6 as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 2.1. The global clotting test PT assesses the extrinsic pathway (coagulation Factors VII, X, V, II, I), of which Factors II, VII, and X are synthesised in the liver. The elevated PT at baseline and a significantly altered sensitivity in anticoagulant activity towards rivaroxaban plasma exposure (increase in slope for PT / rivaroxaban plasma concentration relationship by more than 2-fold) in cirrhotic patients classified as Child Pugh B indicate the decreased ability of the liver to synthesise coagulation factors. The PK/PD changes in these patients are markers for the severity of the underlying hepatic disease which is expected to lead to a subsequent increased bleeding risk in this patient group. Therefore, rivaroxaban is contra-indicated in patients with significant hepatic disease which is associated with coagulopathy leading to a clinically relevant bleeding risk (see Contra-Indications).

No data are available for Child Pugh C patients (see Dosage and Directions for Use and Contra-Indications).

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 (creatinine clearance 80 – 50 mL/min), moderate (creatinine clearance < 50 - 30 mL/min) or severe (creatinine clearance < 30 mL/min) renal impairment, rivaroxaban plasma concentrations

(AUC) were 1.4; 1.5 and 1.6-fold increased respectively as compared to healthy volunteers (see Sections 4.2 and 4.4).

Corresponding increases in pharmacodynamic effects were more pronounced (see Sections 4.2 and 4.4).

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.

Due to the underlying disease patients with severe renal impairment are at an increased risk of both bleeding and thrombosis. Rivaroxaban is to be used with caution in patients with severe renal impairment (see Sections 4.2 and 4.4).

5.3 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 juvenile 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.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Cellulose microcrystalline
- Croscarmellose sodium
- Hydroxypropylmethylcellulose 2910
- Lactose monohydrate
- Macrogol 3350
- Magnesium stearate
- Sodium laurylsulphate
- Titanium dioxide E171
- Polyethylene glycol
- Ferric oxide red E172

6.2 Incompatibilities

Not Applicable

6.3 Shelf life
3 years

6.4 STORAGE INSTRUCTIONS:
Store at or below 30 °C. Protect from light and moisture.
Keep blister strips in the original carton until use.

6.5 Nature and content of container
IXAROLA 10 film-coated tablets are packed in colourless, transparent PP (polypropylene)/aluminium blister strips or colourless, transparent PVC/PVDC/aluminium blister strips containing 5 or 10 tablets per blister. Pack sizes: 5 tablets (1 x 5's blister), 10 tablets (1 x 10's blister), 30 tablets (3 x 10's blister) or 100 tablets (10 x 10's blister).

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product.
No Special Requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION
Bayer (Pty) Ltd
Reg. No.: 1968/011192/07
27 Wrench Road
ISANDO
1609

8. REGISTRATION NUMBER
42/8.2/1046

9. DATE OF AUTHORISATION/RENEWAL OF THE AUTHORISATION
27 January 2010

10. DATE OF REVISION OF THE TEXT

12 May 2022