SCHEDULING STATUS: S4

WARNING: (A) PREMATURE DISCONTINUATION OF IXAROLA INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HAEMATOMA

A. Premature discontinuation of IXAROLA increase the risk of thrombotic events:
Premature discontinuation of any oral anticoagulant, including IXAROLA, increases the risk of thrombotic events. If anticoagulation with IXAROLA is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant [*see Posology and method of administration (4.2), Special Warnings and Precautions (4.4.), and Clinical Studies (5.1 & 5.2)*].

B. Spinal/epidural haematoma:
Epidural or spinal hematomas have occurred in patients treated with IXAROLA who are receiving neuraxial anaesthesia or undergoing spinal puncture. These haematomas may result in long-term or permanent paralysis.
Consider these risks when scheduling patients for spinal procedures.
Factors that can increase the risk of developing epidural or spinal haematomas in these patients include:
• Use of indwelling epidural catheters
• Concomitant use of other drugs that affect haemostasis, such as nonsteroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants
• History of traumatic or repeated epidural or spinal punctures
• History of spinal deformity or spinal surgery
• Optimal timing between the administration of IXAROLA and neuraxial procedures is not known
[see Warnings and Precautions (4.4) and Undesirable effects (4.8)].
Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary *[see Special Warnings and Precautions (4.4)]*.
Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis *(see Special Warnings and precautions (4.4)*

1. NAME OF THE MEDICINE

IXAROLA® 15 Film-coated tablets
IXAROLA® 20 Film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 15 mg film-coated tablet contains 15 mg rivaroxaban.
Excipient with known effect
Contains sugar: Each film-coated tablet contains 24.13 mg lactose (as monohydrate), see section 4.4.

Each 20 mg film-coated tablet contains 20 mg rivaroxaban.
Excipient with known effect
Contains sugar: Each film-coated tablet contains 21.76 mg lactose (as monohydrate), see section 4.4.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

IXAROLA 15: Round, biconvex, red film-coated tablets, 6 mm in diameter, 9 mm radius of curvature, debossed with a triangle over "15" on the top side and the BAYER cross on the bottom side of the tablet.

IXAROLA 20: Round, biconvex, brown red film-coated tablets, 6 mm in diameter, 9 mm radius of curvature, debossed with a triangle over "20" on the top side and the BAYER cross on the bottom side of the tablet.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

IXAROLA 15 and IXAROLA 20 are indicated for:

- Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation (SPAF) with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack.
- Treatment of deep vein thrombosis (DVT) and for the prevention of recurrent deep vein thrombosis (DVT) and pulmonary embolism (PE).
- Treatment of pulmonary embolism (PE) and for the prevention of recurrent pulmonary embolism (PE) and deep vein thrombosis (DVT).

4.2 Posology and method of Administration

Posology

IXAROLA 15 and IXAROLA 20 tablets should be taken with food.

SPAF – Recommended usual dose and frequency of administration:

The recommended dose is one IXAROLA 20 tablet once daily.

For patients with moderate renal impairment (creatinine clearance < 50 to 30 ml/min) the recommended dose is one IXAROLA 15 tablet once daily.

SPAF – Duration of treatment:

Therapy should be continued as long as risk factors for stroke and systemic embolism persist.

SPAF – Missed dose:

If a dose is missed the patient should take IXAROLA 15 or IXAROLA 20 immediately and continue with the once daily intake as recommended on the following day.

The dose should not be doubled to make up for a missed dose within the same day.

SPAF – Maximum daily dose:

The recommended maximum daily dose is one IXAROLA 20 tablet (20 mg rivaroxaban).

DVT and PE treatment – Recommended usual dose and frequency of administration:

The recommended dose for the initial treatment of acute DVT and PE is one IXAROLA 15 tablet **twice daily** for the first three weeks followed by one IXAROLA 20 tablet **once daily** for the continued treatment and the 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 to 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 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.

DVT and PE treatment – Missed dose:

It is essential to adhere to the dosage schedule provided.

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

on the following day.

If a dose is missed during the IXAROLA 20 once daily treatment phase the patient should take IXAROLA 20 immediately to ensure intake of 20 mg per day. The patient should continue with the regular one IXAROLA 20 once daily intake as recommended on the following day.

DVT and PE treatment – Maximum daily dose:

The recommended maximum daily dose is 30 mg during the first 3 weeks of treatment.

In the following treatment phase the recommended maximum daily dose is 20 mg.

Converting from warfarin to IXAROLA 15 or IXAROLA 20:

Warfarin treatment should be stopped and IXAROLA 15 or IXAROLA 20 therapy should be initiated when the INR is ≤ 3,0.

For patients treated for DVT, PE and prevention of recurrence, VKA treatment should be stopped and IXAROLA therapy should be initiated once the INR is ≤ 2.5.

When converting patients from warfarin to IXAROLA 15 or IXAROLA 20, INR values will be falsely elevated after the intake of IXAROLA 15 or IXAROLA 20. The INR is not valid to measure the anticoagulant activity of IXAROLA 15 or IXAROLA 20, and therefore should not be used (see section 4.5).

Converting from IXAROLA 15 or IXAROLA 20 to warfarin:

There is a potential for inadequate anticoagulation during the transition from IXAROLA 15 or IXAROLA 20 to warfarin. Continuous adequate anticoagulation should be ensured during any transition to an alternate anticoagulant. It should be noted that IXAROLA 15 and IXAROLA 20 can contribute to an elevated INR.

In patients converting from IXAROLA 15 or IXAROLA 20 to warfarin, warfarin should be given concurrently until the INR is ≥ 2.0. For the first two days of the conversion period, standard warfarin dosing should be used followed by warfarin dosing guided by INR testing. While patients are on both IXAROLA 15 or IXAROLA 20 and warfarin, the INR should not be tested earlier than 24 hours (after the previous dose but prior to the next dose of IXAROLA 15 or IXAROLA 20). Once IXAROLA 15 or IXAROLA 20 is discontinued INR testing may be done reliably 24 hours after the last dose (see section 4.5 and 5.2)

Converting from parenteral anticoagulants to IXAROLA 15 or IXAROLA 20:

For patients currently receiving a parenteral anticoagulant, start IXAROLA 15 or IXAROLA 20, 0 to 2 hours before the time of the next scheduled administration of the parenteral medicine (e.g. LMWH) or at the time of discontinuation of a continuously administered parenteral medicine (e.g. intravenous unfractionated heparin).

Converting from IXAROLA 15 or IXAROLA 20 to parenteral anticoagulants:

Discontinue IXAROLA 15 or IXAROLA 20 and give the first dose of parenteral anticoagulant at the time that the next IXAROLA 15 or IXAROLA 20 dose would have been taken.

There is no need for monitoring of coagulation parameters during treatment with IXAROLA 15 and IXAROLA 20.

Additional information on special populations:

Patients with hepatic impairment:

IXAROLA 15 and IXAROLA 20 are contra-indicated in patients with hepatic disease with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C. (see section 4.3 and 5.2)

Limited clinical data in patients with moderate hepatic impairment (Child Pugh B) indicate a significant increase in the pharmacological activity.

No clinical data are available for patients with severe hepatic impairment (Child Pugh C) (see 4.3 and 5.2).

Patients with renal impairment:

Limited clinical data for patients with severe renal impairment (creatinine clearance < 30 to15 ml/min) indicate that rivaroxaban plasma levels are significantly increased in this patient population. Therefore IXAROLA 15 or IXAROLA 20 must be used with caution in these patients.

Use of IXAROLA 15 or IXAROLA 20 is not recommended in patients with creatinine clearance < 15 ml/min (see section 4.4 and 5.2)

No dose adjustment is required if IXAROLA 20 is administered in patients with mild (creatinine clearance ≤ 80 to 50 ml/min) renal impairment. For patients with moderate (creatinine clearance < 50 to 30 ml/min) renal impairment the recommended dose is one IXAROLA 15 once daily.

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

- For the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation, the recommended dose is 15 mg once daily (see section 5.2).

- For the treatment of DVT, treatment of PE and prevention of recurrent DVT and PE: patients should be treated with 15 mg twice daily for the first 3 weeks. Thereafter, when the recommended dose is 20 mg once daily, a reduction of the dose from 20 mg once daily to 15 mg once daily should be considered if the patient's assessed risk for bleeding outweighs the risk for recurrent DVT and PE. The recommendation for the use of 15 mg is based on PK modelling and has not been studied in this clinical setting (see sections 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.

Children and adolescents (from birth to 18 years):

Safety and efficacy have not been established in children and adolescents below 18 years in the indication prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.. No data are available.

Body weight:

No dose adjustment is required based on body weight (see section 5.2)

Patients undergoing cardioversion
IXAROLA can be initiated or continued in patients who may require cardioversion.
For transesophageal echocardiogram (TEE) guided cardioversion in patients not previously treated with anticoagulants, IXAROLA treatment should be started at least 4 hours before cardioversion to ensure adequate anticoagulation (see sections 5.1 and 5.2). For all patients, confirmation should be sought prior to cardioversion that the patient has taken IXAROLA as prescribed. Decisions on initiation and duration of treatment should take established guideline recommendations for anticoagulant treatment in patients undergoing cardioversion into account.

Patients with non-valvular atrial fibrillation who undergo PCI (percutaneous coronary intervention) with stent placement
There is limited experience of a reduced dose of 15 mg IXAROLA once daily (or 10 mg IXAROLA once daily for patients with moderate renal impairment [creatinine clearance 30 - 49 ml/min]) in addition to a P2Y12 inhibitor for a maximum of 12 months in patients with non-valvular atrial fibrillation who require oral anticoagulation and undergo PCI with stent placement (see sections 4.4 and 5.1).

Method of administration
IXAROLA is for oral use. The tablets are to be taken with food (see section 5.2).

For patients who are unable to swallow whole tablets, IXAROLA tablet may be crushed and mixed with water or apple puree immediately prior to use and administered orally. After the administration of crushed IXAROLA 15 mg or 20 mg film-coated tablets, the dose should be immediately followed by food.
The crushed IXAROLA 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. After the administration of crushed IXAROLA 15 mg or 20 mg film-coated tablets, the dose should then be immediately followed by enteral feeding (see section 5.2).

4.3 CONTRAINDICATIONS

IXAROLA 15 and IXAROLA 20 are contra-indicated in patients with:
- Hypersensitivity to rivaroxaban or any excipient of the tablets.
- Clinically significant active bleeding (e.g. intracranial bleeding, gastrointestinal bleeding).
- Known existing inherited bleeding disorders.
- Persistent triple positive antiphospholipid syndrome (APS).
- Hepatic disease associated with coagulopathy and 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).

- Safety and efficacy of IXAROLA 15 and IXAROLA 20 have not been established in pregnant women. Animal data show that rivaroxaban crosses the placental barrier. Therefore the use of IXAROLA 15 and IXAROLA 20 are contra-indicated throughout pregnancy (see section 4.6).

- Safety and efficacy of IXAROLA 15 and IXAROLA 20 have not been established in breastfeeding mothers. Animal data indicate that rivaroxaban is secreted into breast milk. Therefore IXAROLA 15 and IXAROLA 20 may only be administered after breastfeeding is discontinued (see section 4.6)

4.4 Special warnings and precautions for use

Clinical surveillance in line with anticoagulation practice is recommended throughout the treatment period.

Patients with prosthetic valves:

IXAROLA 15 and IXAROLA 20 should not be used for thromboprophylaxis in patients having recently undergone transcatheter aortic valve replacement (TAVR). Safety and efficacy of IXAROLA 15 and IXAROLA 20 have not been studied in patients with prosthetic heart valves; therefore, there are no data to support that IXAROLA 20 (IXAROLA 15 in patients with moderate or severe renal impairment) provides adequate anti-coagulation in this patient population. Treatment with IXAROLA 15 and IXAROLA 20 is not recommended.

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).

Patients with non-valvular atrial fibrillation who undergo PCI with stent placement
Clinical data are available from an interventional study with the primary objective to assess safety in patients with non-valvular atrial fibrillation who undergo PCI with stent placement. Data on efficacy in this population are limited (see sections 4.2 and 5.1). No data are available for such patients with a history of stroke/ transient ischaemic attack (TIA).

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

IXAROLA 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 have not been established in these clinical situations.

Bleeding risk:

As with other anticoagulants, patients taking IXAROLA 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 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.

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).
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 5.1 and 5.2).

IXAROLA 15 and IXAROLA 20 should be used with caution in patients with an increased bleeding risk such as:

- Congenital or acquired bleeding disorders
- Uncontrolled severe arterial hypertension
- Vascular retinopathy
- Recent intracranial or intracerebral haemorrhage
- Intraspinal or intracerebral vascular abnormalities
- Shortly after brain, spinal or ophthalmological surgery
- Bronchiectasis or history of pulmonary bleeding.
- other gastrointestinal disease without active ulceration that can potentially lead to bleeding complications (e.g. inflammatory bowel disease, oesophagitis, gastritis and gastroesophageal reflux disease)

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

Surgery and interventions:

If an invasive procedure or surgical intervention is required, IXAROLA 15 and IXAROLA 20 should be stopped at least 24 hours before the intervention, if possible and based on clinical judgement of the medical practitioner.

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

IXAROLA 15 and IXAROLA 20 should be restarted after the invasive procedure or surgical intervention as soon as possible provided the clinical situation allows and adequate haemostasis has been established (see section 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.

Neuraxial (epidural/spinal) 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 or permanent paralysis.

The risk of these events is further increased by post-operative use of indwelling epidural catheters or the concomitant use of medicines affecting haemostasis. The risk may also be increased by traumatic or repeated epidural or spinal punctures.

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 medical practitioner should consider the potential benefit versus the risk before neuraxial intervention in patients who are anticoagulated or considered to be anticoagulated for thromboprophylaxis. There is no clinical experience with the use of IXAROLA 15 and IXAROLA 20 in these situations.

To reduce the potential risk of bleeding associated with the concurrent use of IXAROLA 15 and IXAROLA 20 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. However, the exact timing to reach a sufficiently low anticoagulant effect in each patient is not known.
For the removal of an epidural catheter and based on the general PK characteristics at least 2x half-life, i.e. at least 18 hours in young adult patients and 26 hours in elderly patients should elapse after the last administration of IXAROLA 15 and IXAROLA 20 (see section 5.2). Following removal of the catheter, at least 6 hours should elapse before the next rivaroxaban dose is administered.

If a traumatic puncture occurs, the administration of IXAROLA 15 or IXAROLA 20 should be delayed for 24 hours.

DVT and PE treatment – Renal impairment:

IXAROLA 15 and IXAROLA 20 is to be used with caution in patients with moderate renal impairment (creatinine clearance < 50 to 30 ml/min) receiving co-medications leading to increased rivaroxaban plasma concentrations (see section 4.5).

SPAF, DVT and PE treatment – Renal impairment:

In patients with severe renal impairment (creatinine clearance < 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 the underlying disease these patients are at an increased risk of both bleeding and thrombosis.

Due to limited clinical data IXAROLA 15 and IXAROLA 20 should be used with caution in patients with creatinine clearance < 30 to 15 ml/min.

No clinical data are available for patients with severe renal impairment (creatinine clearance < 15 ml/min). Therefore, the use of IXAROLA 15 and IXAROLA 20 is not recommended in these patients (see section 4.2 and 5.2).

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.

Concomitant medication:

IXAROLA 15 and IXAROLA 20 are not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (e.g. ketoconazole) or HIV protease inhibitors (e.g. ritonavir). These medicines are strong inhibitors of both CYP 3A4 and P-gp. Therefore, these medicines may increase rivaroxaban plasma concentrations to a clinically relevant degree which may lead to an increased bleeding risk (see section 4.5).

The azole anti-mycotic fluconazole, a moderate CYP 3A4 inhibitor, has however less effect on rivaroxaban exposure and can be co-administered (see section 4.5).

Care should be taken if patients are treated concomitantly with medicines affecting haemostasis such as non-steroidal anti-inflammatory medicines (NSAIDs), acetylsalicylic acid and platelet aggregation inhibitors or selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs). (see section 4.5).

For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered (see section 4.5).

Women of childbearing potential:

IXAROLA 15 and IXAROLA 20 should be used in women of childbearing potential only with effective contraception.

QTc prolongation:

No QTc prolonging effect was observed with IXAROLA 15 and IXAROLA 20.

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 rivaroxaban (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 15 and IXAROLA 20 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 15 and IXAROLA 20 contain 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 15 or IXAROLA 20. IXAROLA contains 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:

The concomitant use of IXAROLA 15 or IXAROLA 20 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 IXAROLA 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 C_{max}, with significant increases in its pharmacodynamic effects which may lead to an increased bleeding risk. (see section 4.4)

Co-administration of IXAROLA 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 C_{max}, with significant increases in its pharmacodynamic effects which may lead to an increased bleeding risk. (see section 4.4). Data on the co-administration of IXAROLA with the HIV protease inhibitor ritonavir (100 mg twice daily) is not available.

Therefore IXAROLA 15 and IXAROLA 20 are not recommended in patients receiving concomitant systemic treatment with azole-antimycotics or HIV-protease inhibitors (see section 4.4).

Other active substances strongly inhibiting only one of the rivaroxaban elimination pathways, either CYP 3A4 or P-gp, are expected to increase rivaroxaban plasma concentrations to a lesser extent.

Clarithromycin (500 mg twice daily), considered a strong CYP 3A4 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 AUC and C_{max}. This increase is within the magnitude of the normal variability of AUC and C_{max} and is considered as clinically not relevant.

Fluconazole (400 mg once daily), considered a moderate CYP 3A4 inhibitor, led to a 1,4-fold increase in mean rivaroxaban AUC and a 1,3-fold increase in mean C_{max}. 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.

CYP3A4 inducers
Co-administration of IXAROLA 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 5.2)

The concomitant use of IXAROLA 15 or IXAROLA 20 with other strong CYP 3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbitone or St. John's Wort (*Hypericum perforatum*) may also lead to a decreased rivaroxaban plasma concentration. Strong CYP 3A4 inducers should be co-administered with caution.

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 sections 4.3 and 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 inhibotors
Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) did not show a pharmacokinetic interaction with IXAROLA 15 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 "Warnings").

No clinically relevant prolongation of bleeding time was observed after concomitant administration of IXAROLA 15 and 500 mg naproxen. Nevertheless there may be individuals with more pronounced pharmacodynamic response.

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

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 rivaroxaban clinical programme, numerically higher rates of major or non-major clinically relevant bleeding were observed in all treatment groups.

Warfarin

Converting patients from warfarin (INR 2.0 to 3.0) to IXAROLA 20 or from IXAROLA 20 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 IXAROLA 15 or IXAROLA 20 during the conversion period, anti-Factor Xa activity, prothrombinase-induced clotting time (PiCT), and HepTest® can be used as these tests were not affected by warfarin.

From day 4 after stopping warfarin, all tests (including PT, aPTT, inhibition of factor Xa activity and ETP) reflected only the effect of IXAROLA 15 or IXAROLA 20.

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 IXAROLA.

Interactions shown not to exist:

There were no mutual pharmacokinetic interactions between IXAROLA and midazolam (substrate of CYP 3A4), digoxin (substrate of P-glycoprotein) or atorvastatin (substrate of CYP 3A4 and P-gp).

Co-administration of the proton pump inhibitor omeprazole, the H_2 receptor antagonist ranitidine, the antacid aluminium hydroxide/magnesium hydroxide, naproxen, clopidogrel or enoxaparin did not affect rivaroxaban bioavailability and pharmacokinetics.

Interactions with laboratory parameters:

Clotting parameter tests (PT, aPTT, HepTest®) are affected as expected by the mode of action of IXAROLA 15 and IXAROLA 20.

4.6 Fertility, pregnancy and lactation:

Women of childbearing potential:

IXAROLA 15 and IXAROLA 20 should be used in women of childbearing potential only with effective contraception.

Pregnancy:

Safety and efficacy of IXAROLA 15 and IXAROLA 20 have not been established in pregnant women.

In rats and rabbits rivaroxaban showed pronounced maternal toxicity with placental changes related to its pharmacological mode of action (e.g. haemorrhagic complications) leading to reproductive toxicity. No

primary teratogenic potential was identified. Due to the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, IXAROLA 15 and IXAROLA 20 is contra-indicated in pregnancy (see section 4.3).

Lactation:

Safety and efficacy of IXAROLA 15 and IXAROLA 20 have not been established in nursing mothers. In rats rivaroxaban is secreted into breast milk. Therefore IXAROLA 15 and IXAROLA 20 may only be administered after breastfeeding is discontinued (see section 4.3).

Fertility
No specific studies with IXAROLA 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

Syncope and dizziness have been reported and may affect the ability to drive and use machines (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 venous thromboembolism 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 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 100 mg 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 significant coronary artery disease following an episode of decompensated heart failure	2,499	2.5 mg bid combined with ASA 100 mg	42 months (or >1,260 days)
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

Indication	Number of patients*	Total daily dose	Maximum treatment duration
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

Bleeding and anemia events rates in patients exposed to IXAROLA across the completed phase III studies:

Indication investigated in phase III studies	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 atherothrombotic 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 *
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	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	39.5% of patients	4.6% of patients

in term neonates and children aged less than 18 years following initiation of standard anticoagulation treatment		
Prevention of atherothrombotic events in patients after recent revascularization procedure of the lower limb due to symptomatic PAD	(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.

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 a hemorrhage should be considered in evaluating the condition in any anticoagulated patient.

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 treatment-emergent adverse drug reactions reported in adult patients in phase III studies (pooled RECORD 1-4, ROCKET, J-ROCKET, MAGELLAN, ATLAS, EINSTEIN (DVT/PE/Extension/CHOICE), and COMPASS*, NAVIGATE ESUS* MARINER*, COMMANDER

HF*, CASSINI*, GALILEO*, in two phase II and one phase III study EINSTEIN Junior in pediatric patients, and VOYAGER PAD*)

Common	Uncommon	Rare	Very rare	Not known
Blood and lymphatic system disorders				
Anaemia (incl. respective laboratory parameters)	Thrombocytosis (incl. platelet count increased)[A],			
Immune system disorders				
	Allergic reaction, dermatitis allergic			
Nervous system disorders				
Dizziness, headache	Cerebral and intracranial haemorrhage, syncope			

Common	Uncommon	Rare	Very rare	Not known
Eye disorders				
Eye haemorrhage (incl. conjunctival haemorrhage)				
Cardiac disorders				
	Tachycardia			
Vascular disorders				
Hypotension, haematoma				
Respiratory, thoracic and mediastinal disorders				
Epistaxis, haemoptysis				
Gastrointestinal disorders				
Gingival bleeding, gastrointestinal tract haemorrhage (incl. rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation[A], diarrhoea, vomiting[A]	Dry mouth			
Hepatobiliary disorders				
	Hepatic impairment	Jaundice		

Common	Uncommon	Rare	Very rare	Not known
Skin and subcutaneous tissue disorders				
Pruritus (incl. uncommon cases of generalised pruritus), rash, ecchymosis, cutaneous and subcutaneous haemorrhage	Urticaria			
Musculoskeletal and connective tissue disorders				
Pain in extremity[A]	Haemarthrosis	Muscle haemorrhage		

Common	Uncommon	Rare	Very rare	Not known
Renal and urinary disorders				
Urogenital tract haemorrhage (incl. haematuria and menorrhagia[B]), renal impairment (incl. blood creatinine increased, blood urea increased)[A]				
General disorders and administration site conditions				
Fever[A], peripheral oedema, decreased general strength and energy (incl. fatigue and asthenia)	Feeling unwell (incl. malaise)	Localised oedema[A]		
Investigations				
Increase in transaminases	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)		

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 4.4).
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 4.9 *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 a hemorrhage should 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.

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 Overdose

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 or above.

A specific antidote antagonising the pharmacodynamic effect of IXAROLA 15 and IXAROLA 20 is not available in South Africa. The use of activated charcoal to reduce absorption in case of IXAROLA 15 and IXAROLA 20 overdose may be considered. Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

Management of bleeding:

Should a bleeding complication arise in a patient receiving IXAROLA 15 and IXAROLA 20, the next administration should be delayed or treatment should be discontinued as appropriate. Rivaroxaban has a half-life of approximately 5 to 13 hours (see section 5.2). Management should be individualised according to the severity and location of the haemorrhage. Appropriate symptomatic treatment could be used as needed, such as mechanical compression (e.g. for severe epistaxis), surgical haemostasis with bleeding control procedures, fluid replacement and haemodynamic support, blood products (packed red cells or fresh frozen plasma, depending on associated anaemia or coagulopathy) or platelets.

If bleeding cannot be controlled by the above measures, administration of a specific procoagulant factor Xa inhibitor reversal agent (andexanet alfa) 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 IXAROLA 15 or IXAROLA 20. The recommendation is also based on limited non-clinical data. Re-dosing of recombinant factor VIIa shall be considered and titrated depending on improvement of bleeding. Depending on local availability, a consultation with a coagulation expert should be considered in case of major bleedings (see section 5.1).

Protamine sulphate and Vitamin K are not expected to affect the anticoagulant activity of IXAROLA 15 or IXAROLA 20.

There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving IXAROLA 15 or IXAROLA 20. There is neither scientific rationale for benefit nor experience with the systemic haemostatics desmopressin and aprotinin in individuals receiving IXAROLA 15 or IXAROLA 20. Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.

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:

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 Normalised Ratio) is only calibrated and validated for coumarins and cannot be used for any other anticoagulant.

In patients receiving rivaroxaban for treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE, the 5/95 percentiles for PT (Neoplastin®) 2 to 4 hours after tablet intake (i.e. at the time of maximum effect) ranged from 17 seconds to 32 seconds for 15 mg twice daily or 15 seconds to 30 seconds for 20 mg once daily, respectively.

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

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

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

Clinical efficacy and safety

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

The IXAROLA clinical programme was designed to demonstrate the efficacy of IXAROLA for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

In the pivotal double-blind ROCKET AF study, 14,264 patients were assigned either to IXAROLA 20 mg once daily (15 mg once daily in patients with creatinine clearance 30 - 49 ml/min) or to warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0). The median time on treatment was 19 months and overall treatment duration was up to 41 months.

34.9% of patients were treated with acetylsalicylic acid and 11.4% were treated with class III antiarrhythmic including amiodarone.

IXAROLA was non-inferior to warfarin for the primary composite endpoint of stroke and non-CNS systemic embolism. In the per-protocol population on treatment, stroke or systemic embolism occurred in 188 patients on rivaroxaban (1.71% per year) and 241 on warfarin (2.16% per year) (HR 0.79; 95% CI, 0.66 - 0.96; P<0.001 for non-inferiority). Among all randomised patients analysed according to ITT, primary events occurred in 269 on rivaroxaban (2.12% per year) and 306 on warfarin (2.42% per year) (HR 0.88; 95% CI, 0.74 - 1.03; P<0.001 for non-inferiority; P=0.117 for superiority). Results for secondary endpoints as tested in hierarchical order in the ITT analysis are displayed in Table 4.

Among patients in the warfarin group, INR values were within the therapeutic range (2.0 to 3.0) a mean of 55% of the time (median, 58%; interquartile range, 43 to 71). The effect of rivaroxaban did not differ across the level of centre TTR (Time in Target INR Range of 2.0 - 3.0) in the equally sized quartiles (P=0.74 for interaction). Within the highest quartile according to centre, the Hazrad Ration (HR) with rivaroxaban versus warfarin was 0.74 (95% CI, 0.49 - 1.12).

The incidence rates for the principal safety outcome (major and non-major clinically relevant bleeding events) were similar for both treatment groups (see Table 5).

Table 4: Efficacy results from phase III ROCKET AF

Study population	**ITT analyses of efficacy in patients with non-valvular atrial fibrillation**		
Treatment dose	**IXAROLA 20 mg od (15 mg od in patients with moderate renal impairment) Event rate (100 pt-yr)**	**Warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0) Event rate (100 pt-yr)**	**HR (95% CI) p-value, test for superiority**
Stroke and non-CNS systemic embolism	269 (2.12)	306 (2.42)	0.88 (0.74 - 1.03) 0.117
Stroke, non-CNS systemic embolism and vascular death	572 (4.51)	609 (4.81)	0.94 (0.84 - 1.05) 0.265
Stroke, non-CNS systemic embolism, vascular death and myocardial infarction	659 (5.24)	709 (5.65)	0.93 (0.83 - 1.03) 0.158
Stroke	253 (1.99)	281 (2.22)	0.90 (0.76 - 1.07) 0.221
Non-CNS systemic embolism	20 (0.16)	27 (0.21)	0.74 (0.42 - 1.32) 0.308
Myocardial infarction	130 (1.02)	142 (1.11)	0.91 (0.72 - 1.16) 0.464

Table 5: Safety results from phase III ROCKET AF

Study population	Patients with non-valvular atrial fibrillation[a)]		
Treatment dose	**IXAROLA 20 mg once a day (15 mg once a day in patients with moderate renal impairment) Event rate (100 pt-yr)**	**Warfarin titrated to a target INR of 2.5 (therapeutic range 2.0 to 3.0) Event rate (100 pt-yr)**	**HR (95% CI) p-value**
Major and non-major clinically relevant bleeding events	1,475 (14.91)	1,449 (14.52)	1.03 (0.96 - 1.11) 0.442
Major bleeding events	395 (3.60)	386 (3.45)	1.04 (0.90 - 1.20) 0.576
Death due to bleeding*	27 (0.24)	55 (0.48)	0.50 (0.31 - 0.79) 0.003
Critical organ bleeding*	91 (0.82)	133 (1.18)	0.69 (0.53 - 0.91) 0.007
Intracranial haemorrhage*	55 (0.49)	84 (0.74)	0.67 (0.47 - 0.93) 0.019
Haemoglobin drop*	305 (2.77)	254 (2.26)	1.22 (1.03 - 1.44) 0.019
Transfusion of 2 or more units of packed red blood cells or whole blood*	183 (1.65)	149 (1.32)	1.25 (1.01 - 1.55) 0.044
Non-major clinically relevant bleeding events	1,185 (11.80)	1,151 (11.37)	1.04 (0.96 - 1.13) 0.345
All-cause mortality	208 (1.87)	250 (2.21)	0.85 (0.70 - 1.02) 0.073

a) Safety population, on treatment
* Nominally significant

In addition to the phase III ROCKET AF study, a prospective, single-arm, post-authorization, non-interventional, open-label cohort study (XANTUS) with central outcome adjudication including thromboembolic events and major bleeding has been conducted. 6,785 patients with non-valvular atrial fibrillation were enrolled for prevention of stroke and non-central nervous system (CNS) systemic embolism in clinical practice. The mean $CHADS_2$ and HAS-BLED scores were both 2.0 in XANTUS, compared to a mean $CHADS_2$ and HAS-BLED score of 3.5 and 2.8 in ROCKET AF, respectively. Major bleeding occurred in 2.1 per 100 patient years. Fatal haemorrhage was reported in 0.2 per 100 patient years and intracranial haemorrhage in 0.4 per 100 patient years. Stroke or non-CNS systemic embolism was recorded in 0.8 per 100 patient years.
These observations in clinical practice are consistent with the established safety profile in this indication.

Patients undergoing cardioversion
A prospective, randomised, open-label, multicentre, exploratory study with blinded endpoint evaluation (X-VERT) was conducted in 1504 patients (oral anticoagulant naive and pre-treated) with non-valvular atrial fibrillation scheduled for cardioversion to compare rivaroxaban with dose-adjusted VKA (randomised 2:1), for the prevention of cardiovascular events. TEE- guided (1 - 5 days of pre-treatment) or conventional cardioversion (at least three weeks of pre-treatment) strategies were employed. The primary efficacy outcome (all stroke, transient ischaemic attack, non-CNS systemic embolism, myocardial infarction (MI)

and cardiovascular death) occurred in 5 (0.5%) patients in the rivaroxaban group (n = 978) and 5 (1.0%) patients in the VKA group (n = 492; RR 0.50; 95% CI 0.15-1.73; modified ITT population). The principal safety outcome (major bleeding) occurred in 6 (0.6%) and 4 (0.8%) patients in the rivaroxaban (n = 988) and VKA (n = 499) groups, respectively (RR 0.76; 95% CI 0.21-2.67; safety population). This exploratory study showed comparable efficacy and safety between rivaroxaban and VKA treatment groups in the setting of cardioversion.

Patients with non-valvular atrial fibrillation who undergo PCI with stent placement
A randomised, open-label, multicentre study (PIONEER AF-PCI) was conducted in 2,124 patients with non-valvular atrial fibrillation who underwent PCI with stent placement for primary atherosclerotic disease to compare safety of two rivaroxaban regimens and one VKA regimen. Patients were randomly assigned in a 1:1:1 fashion for an overall 12-month-therapy. Patients with a history of stroke or TIA were excluded. Group 1 received rivaroxaban 15 mg once daily (10 mg once daily in patients with creatinine clearance 30 - 49 ml/min) plus P2Y12 inhibitor. Group 2 received rivaroxaban 2.5 mg twice daily plus DAPT (dual antiplatelet therapy i.e. clopidogrel 75 mg [or alternate P2Y12 inhibitor] plus low-dose acetylsalicylic acid [ASA]) for 1, 6 or 12 months followed by rivaroxaban 15 mg (or 10 mg for subjects with creatinine clearance 30 - 49 ml/min) once daily plus low-dose ASA. Group 3 received dose-adjusted VKA plus DAPT for 1, 6 or 12 months followed by dose-adjusted VKA plus low-dose ASA.
The primary safety endpoint, clinically significant bleeding events, occurred in 109 (15.7%), 117 (16.6%), and 167 (24.0%) subjects in group 1, group 2 and group 3, respectively (HR 0.59; 95% CI 0.47-0.76; $p<0.001$, and HR 0.63; 95% CI 0.50-0.80; $p<0.001$, respectively). The secondary endpoint (composite of cardiovascular events CV death, MI, or stroke) occurred in 41 (5.9%), 36 (5.1%), and 36 (5.2%) subjects in the group 1, group 2 and group 3, respectively. Each of the rivaroxaban regimens showed a significant reduction in clinically significant bleeding events compared to the VKA regimen in patients with non-valvular atrial fibrillation who underwent a PCI with stent placement.
The primary objective of PIONEER AF-PCI was to assess safety. Data on efficacy (including thromboembolic events) in this population are limited.

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 6) rivaroxaban was demonstrated to be non-inferior to enoxaparin/VKA for the primary efficacy outcome ($p < 0.0001$ (test for non-inferiority); 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 6: 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 7) 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 7: 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 8).

Table 8: 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 9) 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 9: 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 (see Table 10) 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 10: 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 (0.0 %)	2 (0.2 %)

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**
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.

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

5.2 Pharmacokinetic properties:

Absorption and bioavailability:

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

The oral bioavailability for the 20 mg tablet dose is 66 %, under fasting conditions. When rivaroxaban 20 mg tablets are taken together with food increases in mean AUC by 39 % were observed when compared to tablet intake under fasting conditions, indicating almost complete absorption and high oral bioavailability. Rivaroxaban 15 mg and 20 mg should be taken with food (see "Dosage and directions for use").

Under fed conditions rivaroxaban 15 mg and 20 mg tablets demonstrated dose-proportionality.

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

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

Bioavailability (AUC and C_{max}) was comparable for 20 mg rivaroxaban administered orally as a crushed tablet mixed in apple puree, or suspended in water and administered via a gastric tube followed by a liquid meal, compared to a whole tablet. 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 other 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 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. 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 substance. 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:

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 (see section 4.2)

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 section 4.2).

Children and adolescents:

Safety and efficacy have not been established for children and adolescents below 18 years in the indication prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (see section 4.2)

Hepatic impairment:

The effect of hepatic impairment on rivaroxaban pharmacokinetics has been studied in subjects categorised according to the Child Pugh classification, a standard procedure in clinical development. In patients for whom anticoagulation is intended, the critical aspect of liver impairment is the reduced synthesis of normal coagulation factors in the liver. Since this aspect is captured by only one of the five clinical/biochemical measurements composing the Child Pugh classification system, the bleeding risk in patients may not clearly correlate with this classification scheme.

Rivaroxaban is contra-indicated in patients with hepatic disease with or without coagulopathy (see section 4.3)

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. There are no data in patients with severe hepatic impairment.

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 that comprises of the coagulation factors VII, X, V, II, I which are synthesised in the liver. Patients with moderate hepatic impairment were more sensitive to rivaroxaban resulting in a steeper PK/PD relationship between concentration and PT.

No data are available for Child Pugh C patients (see section 4.2 and 4.3 IXAROLA is contraindicated in patients with hepatic disease associated with coagulopathy and clinically relevant bleeding risk, including cirrhotic patients with Child Pugh B and C (see section 4.3).

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 to 50 ml/min), moderate (creatinine clearance < 50 to 30 ml/min) or severe (creatinine clearance < 30 to 15 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 section 4.2 and 4.4).

Corresponding increases in pharmacodynamic effects were more pronounced (see section 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.

There are no data in patients with creatinine clearance < 15 ml/min. Use is not recommended in patients with creatinine clearance < 15 ml/min.

Rivaroxaban is to be used with caution in patients with severe renal impairment (creatinine clearance < 30 to 15 ml/min) (see "Warnings" and "Dosage and directions for use"). Due to the underlying disease patients with severe renal impairment are at an increased risk of both bleeding and thrombosis.

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 4.5).

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

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 twice a day). The relationship between rivaroxaban concentration and factor Xa activity was best described by an E_{max} model. For PT, the linear intercept model generally described the data better. Depending on the different PT reagents used, the slope differed considerably. When Neoplastin PT was used, baseline PT was about 13 s and the slope was around 3 to 4 s/(100 mcg/l). The results of the PK/PD analyses in Phase II and III were consistent with the data established in healthy subjects.

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

Tablet core:
Cellulose microcrystalline,

Croscarmellose sodium,

Hypromellose 5 cP,

Lactose monohydrate,

Magnesium stearate,

Sodium lauryl sulphate.

Film-coat:

Ferric oxide red E172,

Hypromellose 15 cP,

Macrogol 3350,

Titanium dioxide E171.

6.2 Incompatibilities

Not Applicable

6.3 Shelf Life

3 years

6.4 Special precautions for storage

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

6.5 Nature and contents of container

IXAROLA 15 film-coated tablets are packed in colourless, transparent PP (polypropylene)/aluminium blister strips or colourless, transparent PVC/PVDC/aluminium blister strips. Pack sizes: 14 tablets, 28 tablets, 42 tablets, 98 tablets or 100 tablets.

IXAROLA 20 film-coated tablets are packed in colourless, transparent PP (polypropylene)/aluminium blister strips or colourless, transparent PVC/PVDC/aluminium blister strips. Pack sizes: 14 tablets, 28 tablets, 42 tablets, 98 tablets or 100 tablets.

6.6 Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product

Any unused medicines or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Bayer (Pty) Ltd
Reg. No.: 1968/011192/07
27 Wrench Road
ISANDO
1609

8. REGISTRATION NUMNER(S)

IXAROLA 15: 46/8.2/0111
IXAROLA 20: 46/8.2/0112

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

05 December 2013

10. DATE OF REVISION OF THE TEXT

12 May 2022