PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

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

A. Premature discontinuation of XABANAR increase the risk of thrombotic events:

Premature discontinuation of any oral anticoagulant, including XABANAR, increases the risk of thrombotic events. If anticoagulation with XABANAR 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), and Special Warnings and Precautions (4.4.)].

B. Spinal/epidural haematoma:

Epidural or spinal hematomas have occurred in patients treated with XABANAR 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 medicines 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 XABANAR 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

XABANAR 10 mg film-coated tablets

XABANAR 15mg film-coated tablets

XABANAR 20 mg film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

XABANAR 10 mg: Each film-coated tablet contains rivaroxaban 10 mg.

Contains sugar lactose monohydrate 26,0 mg per tablet.

Contains sodium 0,59 mg per tablet.

XABANAR 15 mg: Each film-coated tablet contains rivaroxaban 15 mg.

Contains sugar lactose monohydrate 14,62 mg per tablet.

Contains sodium 0,53 mg per tablet.

XABANAR 20 mg: Each film-coated tablet contains rivaroxaban 20 mg.

Contains sugar: lactose monohydrate 19,50 mg per tablet.

Contains sodium 0,63 mg per tablet.

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Film-coated tablet.

XABANAR 10 mg: Round, light red, biconvex film-coated tablets having “A1” debossed on one side and plain on other side.

XABANAR 15 mg: Round, red, biconvex film-coated tablets having “A2” debossed on one side and plain on other side.

XABANAR 20 mg: Dark red coloured, oval shaped, biconvex film coated tablet with “A3” debossed on one side and plain on other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

XABANAR 10 mg is indicated for the prevention of venous thromboembolism (VTE) in patients undergoing major orthopaedic surgery of the lower limbs.

XABANAR 15 mg and XABANAR 20 mg are indicated for:

- Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation (SPAF).
- 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

XABANAR 10 mg

Recommended dose and frequency of administration

The recommended dose is one XABANAR 10 mg 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 XABANAR 10 mg 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.

Special patient populations

Elderly (above 65 years), Gender and Body Weight

No dose adjustment is required for these patient populations.

Children (up to 18 years of age)

The safety and efficacy of XABANAR 10 mg has not been established in children. No clinical data is available for children.

Patients with impaired liver function

XABANAR 10 mg is contraindicated 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

No dose adjustment is required if XABANAR 10 mg is administered in patients with mild (creatinine clearance 80 – 50 ml/min) or moderate (creatinine clearance < 50 - 30 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 XABANAR 10 mg 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).

Ethnic differences

No dose adjustment is required based on ethnic differences.

XABANAR 15 mg and XABANAR 20 mg

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

SPAF - Recommended usual dose and frequency of administration

The recommended dose is one XABANAR 20 mg tablet once daily.

For patients with moderate renal impairment (creatinine clearance < 50 to 30 ml/min) the recommended dose is one XABANAR 15 mg 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 XABANAR 15 mg or XABANAR 20 mg 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 XABANAR 20 mg tablet (20 mg rivaroxaban).

SPAF - Additional information on special populations

SPAF - Patients with hepatic impairment

XABANAR 15 mg and XABANAR 20 mg are contraindicated 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 sections 4.3 and 5.2).

SPAF - Patients with renal impairment

No dose adjustment is required if XABANAR 20 mg 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 XABANAR 15 mg once daily.

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 XABANAR 15 mg must be used with caution in these patients.

Use of XABANAR 15 mg or XABANAR 20 mg is not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.4 and 5.2).

SPAF - Converting from warfarin to XABANAR 15 mg *or* XABANAR 20 mg

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

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

SPAF - Converting from XABANAR 15 mg *or* XABANAR 20 mg *to warfarin*

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

In patients converting from XABANAR 15 mg or XABANAR 20 mg 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 XABANAR 15 mg or XABANAR 20 mg and warfarin, the INR should not be tested earlier than 24 hours (after the previous dose but prior to the next dose of XABANAR 15 mg or XABANAR 20 mg). Once XABANAR 15 mg or XABANAR 20 mg is discontinued INR testing may be done reliably 24 hours after the last dose (see section 4.5).

SPAF - Converting from parenteral anticoagulants to XABANAR 15 mg *or* XABANAR 20 mg

For patients currently receiving a parenteral anticoagulant, start XABANAR 15 mg or XABANAR 20 mg, 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).

SPAF - Converting from XABANAR 15 mg *or* XABANAR 20 mg *to parenteral anticoagulants*

Discontinue XABANAR 15 mg or XABANAR 20 mg and give the first dose of parenteral anticoagulant at the time that the next XABANAR 15 mg or XABANAR 20 mg dose would have

been taken.

SPAF - Children and adolescents (from birth to 18 years)

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

SPAF - Body weight

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

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 XABANAR 15 mg tablet twice daily for the first three weeks followed by one XABANAR 20 mg 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 XABANAR 10 mg once daily, a dose of XABANAR 20 mg once daily should be considered.

DVT and PE treatment - Duration of treatment

The duration of therapy and dose selection should be individualised after careful assessment of the treatment benefit against the risk for haemorrhage (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 XABANAR immediately to ensure intake of 30 mg XABANAR 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 XABANAR 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 XABANAR 15 mg twice daily treatment phase the patient should take XABANAR 15 mg immediately to ensure intake of 30 mg per day. In this case two XABANAR 15 mg tablets may be taken at once. The patient should continue with the regular one XABANAR 15 mg twice daily intake as recommended on the following day.

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

DVT and PE treatment - Additional information on special populations

DVT and PE treatment - Patients with hepatic impairment

XABANAR 15 mg and XABANAR 20 mg are contraindicated 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 sections 4.3 and 5.2).

DVT and PE treatment - Patients with renal impairment

No dose adjustment is required if XABANAR 20 mg 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 XABANAR 15 mg once daily.

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

Use of XABANAR 15 mg and XABANAR 20 mg are not recommended in patients with creatinine clearance < 15 ml/min (see sections 4.4 and 5.2).

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.

DVT and PE treatment - Converting from warfarin to XABANAR 15 mg *or* XABANAR 20 mg.

Warfarin treatment should be stopped and XABANAR 15 mg or XABANAR 20 mg therapy should

be initiated once the INR is ≤ 3,0.

For patients treated for DVT, PE and prevention of recurrence, Vitamin K antagonists (VKA) treatment should be stopped and XABANAR therapy should be initiated once the INR is ≤ 2,5.

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

DVT and PE treatment - Converting from XABANAR 15 mg *or* XABANAR 20 mg *to warfarin.*

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

In patients converting from XABANAR 15 mg or XABANAR 20 mg 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 XABANAR 15 mg or XABANAR 20 mg and warfarin, the INR should not be tested earlier than 24 hours (after the previous dose but prior to the next dose of XABANAR 15 mg or XABANAR 20 mg). Once XABANAR 15 mg or XABANAR 20 mg is discontinued INR testing may be done reliably 24 hours after the last dose (see section 4.5).

DVT and PE treatment - Converting from parenteral anticoagulants to XABANAR 15 mg *or* XABANAR 20 mg

For patients currently receiving a parenteral anticoagulant, start XABANAR 15 mg or XABANAR 20 mg, 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).

DVT and PE treatment - Converting from XABANAR 15 mg *or* XABANAR 20 mg *to parenteral anticoagulants*

Discontinue XABANAR 15 mg or XABANAR 20 mg and give the first dose of parenteral anticoagulant at the time that the next XABANAR 15 mg or XABANAR 20 mg dose would have

been taken.

DVT and PE treatment - Children and adolescents (from birth to 18 years)

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

DVT and PE treatment - Body weight

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

Method of administration

Oral use.

XABANAR 10 mg may be taken with or without food.

XABANAR 15 mg and 20 mg must be taken with food.

4.3 Contraindications

- Hypersensitivity to rivaroxaban or to any of the excipients of XABANAR (see section 6.1).
- Active clinically significant bleeding (e.g. intracranial bleeding, gastrointestinal bleeding).
- Known existing inherited bleeding disorders.
- 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).
- Hepatic disease associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (see section 5.2).
- Pregnancy and breast-feeding (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

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

Haemorrhagic risk

Patients taking XABANAR are to be carefully observed for signs of bleeding. It is recommended to be used with caution in conditions with increased risk of haemorrhage. XABANAR 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 XABANAR 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 below, 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 XABANAR 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).

Renal impairment

In adult patients with severe renal impairment (creatinine clearance < 30 ml/min) rivaroxaban plasma levels may be significantly increased (1,6 fold on average) which may lead to an increased

bleeding risk. XABANAR 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).

XABANAR should be used with caution in patients with renal impairment concomitantly receiving other medicines which increase rivaroxaban plasma concentrations (see section 4.5).

Interaction with other medicines

The use of XABANAR is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics (such as ketoconazole, itraconazole, voriconazole and posaconazole) or HIV protease inhibitors (e.g. ritonavir). These active substances are strong inhibitors of both CYP3A4 and P-gp and therefore may increase rivaroxaban plasma concentrations to a clinically relevant degree (2,6 fold on average) which may lead to an increased bleeding risk (see section 4.5).

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

Other haemorrhagic risk factors

XABANAR is not recommended in patients with an increased bleeding risk such as

- congenital or acquired bleeding disorders
- uncontrolled severe arterial hypertension
- other gastrointestinal disease without active ulceration that can potentially lead to bleeding complications (e.g. inflammatory bowel disease, oesophagitis, gastritis and gastroesophageal reflux disease)
- vascular retinopathy
- bronchiectasis or history of pulmonary bleeding
- active ulcerative gastrointestinal diseases

- recent gastrointestinal ulcerations
- recent intracranial/intracerebral haemorrhage
- shortly after brain, spinal or ophthalmological surgery.

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 tumour location, antineoplastic therapy and stage of disease.

Patients with prosthetic valves

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

Patients with antiphospholipid syndrome

Direct acting Oral Anticoagulants (DOACs) including XABANAR are not recommended for patients with a history of thrombosis who are diagnosed with antiphospholipid syndrome. In particular for patients that are triple positive (for lupus anticoagulant, anticardiolipin antibodies, and anti-beta 2-glycoprotein I antibodies), treatment with DOACs could be associated with increased rates of recurrent thrombotic events compared with vitamin K antagonist therapy.

Hip fracture surgery

Rivaroxaban, as in XABANAR, has not been studied in interventional clinical studies in patients undergoing hip fracture surgery to evaluate efficacy and safety.

Patients with non-valvular atrial fibrillation who undergo percutaneous coronary intervention (PCI) with stent placement

Clinical data are available from an interventional study with the primary objective to assess safety in patients with nonvalvular atrial fibrillation who undergo PCI with stent placement. Data on efficacy in this population are limited. 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

XABANAR 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 XABANAR have not been established in these clinical situations.

Spinal/epidural anaesthesia or puncture

When neuraxial anaesthesia (spinal/epidural anaesthesia) or spinal/epidural puncture is employed, patients treated with antithrombotic medicines for prevention of thromboembolic complications are at risk of developing an epidural or spinal haematoma which can result in long-term or permanent paralysis. The risk of these events may be increased by the 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 puncture. Patients are to be frequently monitored for signs and symptoms of neurological impairment (e.g. numbness or weakness of the legs, bowel or bladder dysfunction). If neurological compromise is noted, urgent diagnosis and treatment is necessary. Prior to neuraxial intervention the medical practitioner should consider the potential benefit versus the risk in anticoagulated patients or in patients to be anticoagulated for thromboprophylaxis. There is no clinical experience with the use of 15 mg and 20 mg rivaroxaban (as in XABANAR) in these situations.

To reduce the potential risk of bleeding associated with the concurrent use of XABANAR 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 patients and 26 hours in elderly patients should elapse after the last administration of XABANAR (see section 5.2). Following removal of the catheter, at least 6 hours should elapse before the next XABANAR dose is administered. If traumatic puncture occurs the administration of XABANAR is to be delayed for 24 hours.

Dosing recommendations before and after invasive procedures and surgical intervention

If an invasive procedure or surgical intervention is required, XABANAR should be stopped at least 24 hours before the intervention, if possible and based on the 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. XABANAR 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 medical practitioner (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 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. XABANAR 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

XABANAR contains lactose monohydrate. Patients with the rare hereditary conditions of galactose intolerance total lactase deficiency or glucose-galactose malabsorption should not take XABANAR.

XABANAR contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction

CYP3A4 and P-gp inhibitors

Co-administration of rivaroxaban with ketoconazole (400 mg once a day) or ritonavir (600 mg twice a day) led to a 2,6 fold / 2,5 fold increase in mean rivaroxaban AUC and a 1,7 fold / 1,6 fold increase in mean rivaroxaban C_{max}, with significant increases in pharmacodynamic effects which may lead to an increased bleeding risk. Therefore, the use of XABANAR 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).

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 a day), which inhibits CYP3A4 and P-gp moderately, led to a 1,3-fold increase in mean rivaroxaban (as in XABANAR) AUC and C_{max}. The interaction with erythromycin is likely not clinically relevant in most patients 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 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 XABANAR should be avoided.

Anticoagulants

After combined administration of enoxaparin (40 mg single dose) with rivaroxaban, as in XABANAR, (10 mg single dose) an additive effect on anti-factor Xa activity was observed without any additional effects on clotting tests (PT, aPTT). Enoxaparin did not affect the pharmacokinetics of rivaroxaban.

Due to the increased bleeding risk care is to be taken if patients are treated concomitantly with any other anticoagulants (see sections 4.3 and 4.4).

NSAIDs/platelet aggregation inhibitors

No clinically relevant prolongation of bleeding time was observed after concomitant administration of rivaroxaban, as in XABANAR, (10 mg and 15 mg) and 500 mg naproxen. Nevertheless, there may be individuals with a more pronounced pharmacodynamic response.

No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when rivaroxaban was co-administered with 500 mg acetylsalicylic acid. Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) did not show a pharmacokinetic interaction with rivaroxaban, as in XABANAR, (10 mg and 15 mg) but a relevant increase in bleeding time was observed in a subset of patients which was not correlated to platelet aggregation, P-selectin or GPIIb/IIIa receptor levels.

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

SSRIs/SNRIs

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 XABANAR 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 rivaroxaban (20 mg) or from rivaroxaban (20 mg) to warfarin (INR 2,0 to 3,0) increased prothrombin time/INR (Neoplastin) more than additively (individual INR values up to 12 may be observed), whereas effects on aPTT, inhibition of factor Xa activity and endogenous thrombin potential were additive.
If it is desired to test the pharmacodynamic effects of rivaroxaban during the conversion period, anti-factor Xa activity, PiCT, and Heptest can be used as these tests were not affected by warfarin. On the fourth day after the last dose of warfarin, all tests (including PT, aPTT, inhibition of factor Xa activity and ETP) reflected only the effect of rivaroxaban.
If it is desired to test the pharmacodynamic effects of warfarin during the conversion period, INR measurement can be used at the C_{trough} of rivaroxaban (24 hours after the previous intake of rivaroxaban) as this test is minimally affected by rivaroxaban at this time point.
No pharmacokinetic interaction was observed between warfarin and rivaroxaban.

CYP3A4 inducers

Co-administration of rivaroxaban with the strong CYP3A4 inducer rifampicin led to an approximate 50 % decrease in mean rivaroxaban AUC, with parallel decreases in its pharmacodynamic effects. The concomitant use of XABANAR with other strong CYP3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbital or St. John's Wort (*Hypericum perforatum*)) may also lead to

reduced rivaroxaban (as in XABANAR) 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). Rivaroxaban neither inhibits nor induces any major CYP isoforms like CYP3A4.

Laboratory parameters

Clotting parameters (e.g. PT, aPTT, HepTest) are affected as expected by the mode of action of rivaroxaban, as in XABANAR (see section 5.1).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should avoid becoming pregnant during treatment with XABANAR. XABANAR should be used in women of childbearing potential only with effective contraception.

Pregnancy

Safety and efficacy of XABANAR have not been established in pregnant women. Studies in animals have shown reproductive toxicity. Due to the potential reproductive toxicity, the intrinsic risk of bleeding and the evidence that Rivaroxaban passes the placenta, XABANAR is contraindicated during pregnancy (see section 4.3).

Breastfeeding

Safety and efficacy of XABANAR have not been established in breastfeeding women. Data from animals indicate that rivaroxaban is secreted into breast milk. Therefore, XABANAR is contraindicated during breastfeeding (see section 4.3).

Fertility

No specific studies with XABANAR in humans have been conducted to evaluate effects on fertility.

4.7 Effects on ability to drive and use machines

Adverse reactions like syncope and dizziness have been reported (see section 4.8). Patients experiencing these adverse reactions should not drive or use machines.

4.8 Undesirable effects

a. Summary of the safety profile

The safety of rivaroxaban has been evaluated in twenty phase III studies including 70 021 patients exposed to rivaroxaban.

b. Tabulated summary of adverse reactions

The frequencies of adverse reactions reported with XABANAR are summarised in the table below by system organ class and by frequency.

System organ class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Frequent	Anaemia (incl. respective laboratory parameters)
	Less frequent	Thrombocytosis (incl. platelet count increased)[A], thrombocytopenia
Immune system disorders	Less frequent	Allergic reaction, dermatitis allergic, angioedema and allergic oedema, anaphylactic reactions including anaphylactic shock

Nervous system disorders	Frequent	Dizziness, headache
	Less frequent	Syncope, cerebral and intracranial haemorrhage, syncope
Eye disorders	Frequent	Eye haemorrhage (incl. conjunctival haemorrhage)
Cardiac disorders	Less frequent	Tachycardia
Vascular disorders	Frequent	Hypotension, haematoma
Respiratory, thoracic and mediastinal disorders	Frequent	Epistaxis, haemoptysis
Gastrointestinal disorders	Frequent	Gingival bleeding, gastrointestinal tract haemorrhage (incl. rectal haemorrhage), gastrointestinal and abdominal pains, dyspepsia, nausea, constipation[A], diarrhoea, vomiting[A]
	Less frequent	Dry mouth
Hepato-biliary disorders	Frequent	Increase in transaminases
	Less frequent	Jaundice, cholestasis, hepatitis (incl. hepatocellular injury) hepatic impairment, increased bilirubin, increased blood alkaline phosphatase[A], increased GGT[A], bilirubin conjugated increased (with or without concomitant increase of ALT)
Skin and subcutaneous tissue disorders	Frequent	Pruritus (incl. uncommon cases of generalised pruritus), rash, ecchymosis, cutaneous and subcutaneous haemorrhage

	Less frequent	Urticaria, Stevens-Johnson syndrome/ toxic epidermal necrolysis, DRESS syndrome
Musculoskeletal and connective tissue disorders	Frequent	Pain in extremity[A],
	Less frequent	Haemarthrosis, muscle haemorrhage
	Frequency Unknown	Compartment syndrome secondary to a bleeding
Renal and urinary disorders	Frequent	Urogenital tract haemorrhage (incl. haematuria and menorrhagia[B]), renal impairment (incl. blood creatinine increased, blood urea increased)
	Frequency Unknown	Renal failure/acute renal failure secondary to a bleeding sufficient to cause hypoperfusion
General disorders and administration site conditions	Frequent	Fever[A], peripheral oedema, decreased general strength and energy (incl. fatigue and asthenia)
	Less frequent	Feeling unwell (incl. malaise), localised oedema[A]
Investigations	Less frequent	Increased LDH[A], increased lipase[A], increased amylase[A]
Injury, poisoning and procedural complications	Frequent	Postprocedural haemorrhage (incl. postoperative anaemia, and wound haemorrhage), contusion
	Less frequent	Vascular pseudoaneurysm[C] , wound secretion[A]

A: observed in prevention of VTE in adult patients undergoing elective hip or knee replacement surgery.

B: observed in treatment of DVT, PE and prevention of recurrence as very common in women

< 55 years.

C: observed as uncommon in prevention of atherothrombotic events in patients after an ACS (following percutaneous coronary intervention).

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

c. Description of selected adverse reactions

Due to the pharmacological mode of action, the use of XABANAR may be associated with an increased risk of occult or overt bleeding from any tissue or organ which may result in post haemorrhagic anaemia. The signs, symptoms, and severity (including fatal outcome) will vary according to the location and degree or extent of the bleeding and/or anaemia (see section 4.9 “Management of bleeding”). 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. The risk of bleedings may be increased in certain patient groups, e.g. those patients with uncontrolled severe arterial hypertension and/or on concomitant treatment affecting haemostasis (see section 4.4 “Haemorrhagic risk”). Menstrual bleeding may be intensified and/or prolonged. Haemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnoea and unexplained shock. In some cases as a consequence of anaemia, symptoms of cardiac ischaemia like chest pain or angina pectoris have been observed.

Known complications secondary to severe bleeding such as compartment syndrome and renal failure due to hypoperfusion have been reported for XABANAR. Therefore, the possibility of haemorrhage is to be considered in evaluating the condition in any anticoagulated patient.

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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

In case of overdose, observe your patients carefully for bleeding complications or other adverse reactions. Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg or above. A specific reversal medicine antagonising the pharmacodynamic effect of rivaroxaban is not available. The use of activated charcoal to reduce absorption in case of rivaroxaban overdose may be considered. Due to high plasma protein binding rivaroxaban is not expected to be dialysable.

Management of bleeding

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

If bleeding cannot be controlled by the above measures, administration of a specific procoagulant reversal medicine, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC) or recombinant factor VIIa (r-FVIIa), should be considered.

However, there is currently very limited clinical experience with the use of these medicines in individuals receiving rivaroxaban.

Protamine sulphate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban (as in XABANAR). There is limited experience with tranexamic acid and no experience with aminocaproic acid and aprotinin in individuals receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with the use of the systemic haemostatic desmopressin in individuals receiving rivaroxaban.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological classification A. 8.2 Anticoagulants.

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 1 000 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 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 thromboplastin 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.
There is no need for monitoring of coagulation parameters during treatment with rivaroxaban in clinical routine.

5.2 Pharmacokinetic properties

Absorption and bioavailability

Rivaroxaban is rapidly absorbed with maximum concentrations (C_{max}) appearing 2 - 4 hours after tablet intake. The absolute bioavailability of rivaroxaban is approximately 100 % for the 10 mg dose. 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.
Administration of rivaroxaban 10 mg 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 section 4.2).
Under fed conditions rivaroxaban 15 mg and 20 mg tablets demonstrated dose-proportionality.
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 Vss being approximately 50 L.

Biotransformation and Elimination

Of the administered rivaroxaban dose, approximately 2/3 undergoes metabolic degradation, with half then being eliminated renally and the other half eliminated by the faecal route. The 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 CYP3A4, CYP2J2 and CYP-independent mechanisms. Oxidative degradation of the morpholinone moiety and hydrolysis of the amide bonds are the major sites of biotransformation. Based on *in vitro* investigations rivaroxaban is a substrate of the transporter proteins P-gp (P-glycoprotein) and Bcrp (breast cancer resistance protein). Unchanged rivaroxaban is the most important compound in human plasma, with no major or active circulating metabolites being present. With a systemic clearance of about 10 L/h, rivaroxaban can be classified as a low-clearance substance. Elimination of rivaroxaban from plasma occurs with terminal half-lives of 5 to 9 hours in young individuals, and with terminal half-lives of 11 to 13 hours in the elderly.

Special populations

Gender

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

Elderly population

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 or > 120 kg) had only a small influence on Rivaroxaban plasma concentrations (less than 25 %). No dose adjustment is necessary.

Inter-ethnic differences

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

Hepatic impairment

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. 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. The inhibition of factor Xa activity was increased by a factor of 2,6 in patients with moderate hepatic impairment as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 2,1. 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 contraindicated in patients with significant hepatic disease which is associated with coagulopathy leading to a clinically relevant bleeding risk (see section 4.3).

No data are available for Child Pugh C patients (see sections 4.2 and 4.3).

Renal impairment

There was an increase in rivaroxaban exposure correlated to decrease in renal function, as assessed via creatinine clearance measurements. In individuals with mild (creatinine clearance 80 - 50 ml/min), moderate (creatinine clearance < 50 ml/min) and severe (creatinine clearance < 30 – 15 ml/min) renal impairment, rivaroxaban plasma concentrations (AUC) were increased 1,4, 1,5 and 1,6 fold respectively as compared to healthy volunteers (see sections 4.2 and 4.4). Corresponding increases in pharmacodynamic effects were more pronounced.

In individuals with mild, moderate and severe renal impairment the overall inhibition of factor Xa activity was increased by a factor of 1,5, 1,9 and 2,0 respectively as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 1,3, 2,2 and 2,4 respectively. There are no data in patients with creatinine clearance < 15 ml/min. Use is not recommended in patients with creatinine clearance < 15 ml/min. Rivaroxaban is to be used with caution in patients with creatinine clearance < 30 - 15 ml/min (see sections 4.2 and 4.4). Due to the underlying disease patients with severe renal impairment are at an increased risk of both bleeding and thrombosis.

Paediatric population

Safety and efficacy have not been established for children and adolescents up to 18 years. No data is available for this patient population (see section 4.2).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core

Croscarmellose sodium

Hypromellose 2910

Lactose monohydrate

Magnesium stearate

Microcrystalline cellulose

Sodium lauryl sulphate

Film-coat (10 mg and 15 mg)

Hypromellose 2910

Iron oxide red (E 172)

Macrogol/ Polyethylene glycol

Titanium dioxide (E 171)

Film-coat (20 mg)

Iron oxide red (E 172)

Macrogol/ Polyethylene glycol

Polyvinyl alcohol

Talc

Titanium dioxide (E 171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

36 months.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep in the original package until required for use.

6.5 Nature and contents of container

XABANAR film-coated tablets are packed in the following containers

- Bottle pack

Round, white opaque high-density polyethylene (HDPE) container with child resistant closure.

- Alu-Alu blister pack

Cold forming blister aluminium foil as forming foil and aluminium foil with heat seal lacquer coat as lidding foil.

- Aluminium-PVC /PVdC blister pack

Plain aluminium foil heat seal lacquer and transparent PVC/PVdC film.

Pack size: 30’s or 100’s.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Trinity Pharma (Pty) Ltd.

106 16th Road

Midrand

1686

8 REGISTRATION NUMBERS

XABANAR 10 mg: 56/8.2/0217

XABANAR 15 mg: 56/8.2/0218

XABANAR 20 mg: 56/8.2/0219

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

08 August 2023

10 DATE OF REVISION OF THE TEXT

Not applicable