INVAROX FILM-COATED TABLET 2.5 MG

1. NAME OF THE MEDICINAL PRODUCT

INVAROX FILM-COATED TABLET 2.5MG

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

INVAROX 2.5 MG
1 film-coated tablet contains 2.5 mg rivaroxaban.
Each 2.5 mg film-coated tablet contains 29.00 mg lactose per tablet.

For a full list of excipient(s) see section 'List of excipients'.

3. PHARMACEUTICAL FORM

INVAROX 2.5 MG
Light yellow, round biconvex tablets, debossed with "2.5" on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Indications

INVAROX, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of cardiovascular death in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers (*see sections 'Contraindications', 'Special warnings and precautions for use' and 'Pharmacodynamic properties'*).

INVAROX, in combination with aspirin, is indicated to reduce the risk of major cardiovascular events (cardiovascular (CV) death, myocardial infarction (MI) and stroke) in adult patients with chronic coronary artery disease (CAD) or peripheral artery disease (PAD) at high risk of ischemic events.

4.2 Dosage and method of administration

4.2.1 Method of administration

Oral use

4.2.2 Recommended usual dose

ACS

The recommended vascular protection regimen is one tablet of 2.5 mg INVAROX twice daily. Patients should also take a daily dose of 75-100 mg ASA or a daily dose 75-100 mg ASA in addition to either a daily dose of 75 mg clopidogrel or a standard daily dose of ticlopidine.

CAD or PAD

The recommended vascular protection regimen for patients with CAD or PAD is one tablet of 2.5 mg INVAROX twice daily in combination with a daily dose of 75-100 mg ASA.

4.2.3 Duration of treatment

Treatment should be regularly evaluated in the individual patient weighing the risk for ischaemic events against the bleeding risks. In patients with ACS, extension of treatment beyond 12 months should be done on an individual patient basis as experience up to 24 months is limited (*see section 'Pharmacodynamic properties'*).

In patients with an acute thrombotic event or vascular procedure and a need for dual antiplatelet therapy, the continuation of INVAROX 2.5 mg twice daily should be evaluated depending on type of event or procedure and antiplatelet regimen. Safety and efficacy of INVAROX 2.5 mg twice daily in combination with ASA plus clopidogrel/ticlopidine has only been studied in patients with recent ACS. Dual antiplatelet therapy has not been studied in combination with INVAROX 2.5 mg twice daily in patients with CAD or PAD (*see section 'Pharmacodynamic properties'*).

4.2.4 Method and frequency of administration

Treatment with INVAROX should be started as soon as possible after stabilization of the ACS event (including revascularization procedures); at the earliest 24 hours after admission to hospital and at the time when parenteral anticoagulation therapy would normally be discontinued.

In patients diagnosed with CAD or PAD, treatment with INVAROX 2.5 mg twice daily in combination with ASA 75-100 mg once daily can be started at any time. One 2.5 mg tablet of INVAROX should be taken twice daily.

INVAROX 2.5 mg tablets may be taken with or without food.

For patients who are unable to swallow whole tablets, INVAROX tablet may be crushed and mixed with water or soft foods such as applesauce immediately prior to use and administered orally.

The crushed INVAROX tablet may be given through gastric tubes. Gastric placement of the tube should be confirmed before administering INVAROX. The crushed tablet should be administered in a small amount of water via a gastric tube after which it should be flushed with water (*see section 'Pharmacokinetic properties'*).

4.2.5 Missed Dose

If a dose is missed the patient should continue with the regular 2.5 mg INVAROX dose as recommended at the next scheduled time. The dose should not be doubled to make up for a missed dose.

4.2.6 Additional information on special populations

4.2.6.1 Patients with hepatic impairment

INVAROX is contraindicated in patients with hepatic disease which is associated with coagulopathy and clinically relevant bleeding risk including cirrhotic patients with Child Pugh B and C (*see section 'Contraindications' and 'Pharmacokinetic properties'*).

No dose adjustment is necessary in patients with other hepatic diseases (*see section 'Pharmacokinetic Properties'*).

4.2.6.2 Patients with renal impairment

No dose adjustment is required if INVAROX is administered in patients with mild (Creatinine clearance (CrC): 80-50 mL/min) or moderate (CrC: <50-30 mL/min) renal impairment (*see section 'Pharmacokinetic Properties'*).

Limited clinical data for patients with severe renal impairment (CrC: <30-15 mL/min) indicate that rivaroxaban plasma levels are significantly increased in this patient population. Therefore INVAROX must be used with caution in these patients (*see section 'Special Warnings and Precautions for Use', 'Pharmacokinetic Properties'*).

Use of INVAROX is not recommended in patients with CrC: <15 mL/min. (*see section 'Special Warnings and Precautions for Use', 'Pharmacokinetic Properties'*).

4.2.6.3 Converting from Vitamin K Antagonists (VKA) to INVAROX

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

4.2.6.4 Converting from INVAROX to Vitamin K antagonists (VKA)

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

In patients converting from INVAROX to VKA, VKA should be given concurrently until the INR is ≥2.0. For the first two days of the conversion period, standard initial VKA dosing should be used followed by VKA dosing guided by INR testing. While patients are on both INVAROX and VKA, the INR should not be tested earlier than 24hours (after the previous dose but prior to the next dose of INVAROX. Once INVAROX is discontinued INR testing may be done reliably 24 hours after the last dose (*see section 'Interaction with other medicinal products and other forms of interaction'*).

4.2.6.5 Converting from parenteral anti-coagulants to INVAROX

For patients currently receiving a parenteral anticoagulant, INVAROX should be started 0 to 2 hours before the time of the next scheduled administration of the parenteral medicinal drug (e.g. low molecular weight heparins) or at the time of discontinuation of a continuously administered parenteral drug (e.g. intravenous unfractionated heparin).

4.2.6.6 Converting from INVAROX to parenteral anti-coagulants

Give the first dose of parenteral anticoagulant at the time that the next INVAROX dose would be

taken.

4.2.6.7 Paediatric population

The safety and efficacy of INVAROX in children aged 0 to 18 years have not been established. No data are available. Therefore, INVAROX is not recommended for use in children below 18 years of age.

4.2.6.8 Geriatric patients

No dose adjustment is required based on age. The risk of bleeding increases with increasing age (*see section 'Pharmacokinetic Properties and Special warnings and precautions for use'*).

4.2.6.9 Gender

No dose adjustment is required based on gender (*see section 'Pharmacokinetic Properties'*).

4.2.6.10 Body weight

No dose adjustment is required based on body weight (*see section 'Pharmacokinetic Properties and Special warnings and precautions for use'*).

4.2.6.11 Ethnic differences

No dose adjustment is required based on ethnic differences (*see section 'Pharmacokinetic Properties'*).

4.3 Contraindications

INVAROX is contraindicated in patients with hypersensitivity to rivaroxaban or any excipient of the tablet (*see section 'Pharmaceutical Particulars'*).

INVAROX is contraindicated in patients with clinically significant active bleeding (e.g., intracranial bleeding, gastrointestinal bleeding).

INVAROX 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 'Pharmacokinetic properties'*).

INVAROX is contraindicated for concomitant treatment of ACS with antiplatelet therapy in patients with a prior stroke or a transient ischaemic attack (TIA) (*see section 'Special warnings and precautions for use'*).

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

Concomitant treatment with any other anticoagulant agent e.g. unfractionated heparin (UFH), low

molecular weight heparins (enoxaparin, dalteparin, etc.), heparin derivatives (fondaparinux, etc.), oral anticoagulants (warfarin, apixaban, dabigatran, etc.) except under the circumstances of switching therapy to or from rivaroxaban (*see section Dosage and administration*) or when UFH is given at doses necessary to maintain an open central venous or arterial catheter (*see section Interaction with other medicinal products and other forms of interaction*).

Safety and efficacy of INVAROX have not been established in pregnant women. Animal data show that rivaroxaban crosses the placental barrier. Therefore use of INVAROX is contraindicated throughout pregnancy (*see section 'Pregnancy and Lactation', 'Preclinical Safety Data'*).

Safety and efficacy of INVAROX have not been established in nursing mothers. Animal data indicate that rivaroxaban is secreted into breast milk. Therefore INVAROX may only be administered after breastfeeding is discontinued (*see section 'Pregnancy and Lactation', 'Preclinical Safety Data'*).

4.4 Special warnings and precautions for use

4.4.1 Patients with prosthetic heart valves

INVAROX is not recommended for thromboprophylaxis in patient having recently undergone transcatheter aortic valve replacement (TAVR) based on data from a randomized controlled clinical study comparing a INVAROX -regimen to an antiplatelet regimen.

The safety and efficacy of INVAROX have not been studied in patients with other prosthetic heart valves or other valve procedures; therefore, there are no data to support that INVAROX provides adequate anticoagulation in those patient populations.

4.4.2 Haemorrhagic risks

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

In the clinical studies mucosal bleedings (i.e. epistaxis, gingival, gastrointestinal, genito urinary) and anaemia were seen more frequently during long term rivaroxaban treatment on top of single or dual anti-platelet therapy. Thus, in addition to adequate clinical surveillance, laboratory testing of haemoglobin/haematocrit could be of value to detect occult bleeding, as judged to be appropriate.

Several sub-groups of patients, as detailed below, are at increased risk of bleeding. Therefore, the use of INVAROX in combination with dual antiplatelet therapy in patients at known increased risk for bleeding should be balanced against the benefit in terms of prevention of cardiovascular death. In addition these patients are to be carefully monitored for signs and symptoms of bleeding complications and anaemia after initiation of treatment (*see section 'Undesirable effects'*).

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

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

4.4.3 Concomitant medication

INVAROX is not recommended in patients receiving concomitant systemic treatment with azole- antimycotics (e.g. ketoconazole) or HIV protease inhibitors (e.g. ritonavir). These drugs are strong inhibitors of both CYP 3A4 and P-gp. Therefore, these drugs may increase rivaroxaban plasma concentrations to a clinically relevant degree (2.6-fold on average) which may lead to an increased bleeding risk.

The Azole-antimycotic fluconazole, a moderate CYP3A4 inhibitor, has however less effect on rivaroxaban exposure and can be co-administered (*see section 'Interaction with other Medicinal Products and other Forms of Interaction')*.

4.4.4 Renal impairment

INVAROX is to be used with caution in patients with moderate renal impairment (CrC: <50-30 mL/min) receiving co-medications leading to increased rivaroxaban plasma concentrations (*see section 'Interaction with other Medicinal Products and other Forms of Interaction'*).

In patients with severe renal impairment (CrC: <30 mL/min) rivaroxaban plasma levels may be significantly elevated (1.6-fold on average) which may lead to an increased bleeding risk. Due to the underlying disease these patients are at an increased risk of both bleeding and thrombosis. Due to limited clinical data INVAROX should be used with caution in patients with CrC <30-15 mL/min. (see *'Pharmacokinetic Properties'*).

No clinical data are available for patients with severe renal impairment (CrC: <15 mL/min). Therefore use of INVAROX is not recommended in these patients (*see sections 'Dosage and Method of Administration'and 'Pharmacokinetic Properties'*).

Patients with severe renal impairment or increased bleeding risk and patients receiving concomitant systemic treatment with azole-antimycotics or HIV protease inhibitors are to be carefully monitored for signs of bleeding complications after initiation of treatment. This may be done by regular physical examination of the patients, close observation of the surgical wound drainage and periodic measurements of hemoglobin (*see section 'Interaction with other Medicinal Products and other Forms of Interaction'*).

4.4.5 Patients with prior stroke and/or TIA

ACS

INVAROX 2.5 mg twice daily is contraindicated for the treatment of ACS in patients with a prior stroke or TIA (*see section 'Contraindications'*). Few ACS patients with a prior stroke or TIA have been studied but the limited efficacy data available indicate that these patients do not benefit from treatment.

CAD or PAD

Patients with haemorrhagic or lacunar stroke

CAD or PAD patients with previous haemorrhagic or lacunar stroke were not studied. Treatment with INVAROX 2.5 mg twice daily in combination with ASA should be avoided in these patients.

Patients with ischemic, non-lacunar stroke

CAD or PAD patients who have experienced an ischemic, non-lacunar stroke within the previous month were not studied. Treatment with INVAROX 2.5 mg twice daily in combination with ASA should be avoided in the first month after stroke (*see section 'Pharmacodynamic properties'*).

4.4.6 Bleeding risk

INVAROX like other antithrombotics should be used with caution in patients with an increased bleeding risk such as:

- congenital or acquired bleeding disorders
- uncontrolled severe arterial hypertension
- active ulcerative gastrointestinal disease
- vascular retinopathy
- bronchiectasis or history of pulmonary bleeding

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

INVAROX should be used with caution in ACS and CAD/PAD patients co-administered with ASA alone or with ASA plus clopidogrel or ticlopidine:

- >75 years of age. The benefit-risk of the treatment should be individually assessed on a regular basis.
- with low body weight (<60kg)

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

Patients on treatment with INVAROX and ASA or with INVAROX and ASA plus clopidogrel/ticlopidine should only receive chronic concomitant treatment with NSAIDS, if the benefit outweighs the bleeding risk.

For patients at risk of ulcerative gastrointestinal disease an appropriate prophylactic treatment may be considered (*see section 'Interaction with other Medicinal Products and other Forms of Interaction'*).

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

In ACS patients efficacy and safety of rivaroxaban 2.5mg twice daily has been investigated in combination with the antiplatelet agents ASA alone or ASA plus clopidogrel/ticlopidine.

Treatment in combination with other antiplatelet agents, e.g. prasugrel or ticagrelor, has not been studied and is not recommended.

4.4.7.1 ACS, CAD or PAD: Neuraxial (epidural/spinal) anesthesia

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

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

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

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

There is no clinical experience with the use of INVAROX 2.5mg twice daily with ASA alone or with ASA plus clopidogrel or ticlopidine in these situations.

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

The concomitant use of platelet aggregation inhibitors should be considered and such medication discontinued as appropriate.

4.4.7.2 Surgery and interventions

If an invasive procedure or surgical intervention is required, INVAROX 2.5 mg should be stopped at least 12 hours before the intervention, if possible and based on clinical judgment of the physician.
If a patient concomitantly receiving platelet aggregation inhibitor is to undergo elective surgery and anti-platelet effect is not desired, platelet aggregation inhibitors should be discontinued as directed by the manufacturer's prescribing information.
If the procedure cannot be delayed the increased risk of bleeding should be assessed against the urgency of the intervention.
INVAROX should be restarted as soon as possible after the invasive procedure or surgical intervention provided the clinical situation allows and adequate hemostasis has been established (*see section 'Pharmacokinetic Properties'*).

4.4.8 Patients with high risk triple positive antiphospholipid syndrome

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

4.4.9 Women of childbearing potential

INVAROX should be used in women of childbearing potential only with effective contraception.

4.4.10 QTc prolongation

No QTc prolonging effect was observed with rivaroxaban *(see section 'Pharmacokinetic Properties')*.

4.4.11 Information about excipients

Since this medicinal product contains lactose, patients with rare hereditary problems of lactose or galactose intolerance (e.g., the Lapp lactase deficiency or glucose-galactose malabsorption) should not take INVAROX (*see section 'Qualitative and quantitative composition'*).

4.5 Interaction with other medicinal products and other forms of interaction

4.5.1 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.

4.5.1.1 CYP Inhibition

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

4.5.1.2 CYP Induction

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

4.5.1.3 Effects on rivaroxaban

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

Co-administration of INVAROX 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.
Co-administration of INVAROX 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.

Therefore INVAROX is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics or HIV-protease inhibitors (*see section 'Special Warnings and Precautions for Use'*).

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 as 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}. This increase, which is close to the magnitude of the normal variability of AUC and C_{max}, is considered as clinically not relevant.

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.

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

Fluconazole (400 mg once daily), considered as moderate CYP 3A4 inhibitor, led to a 1.4-fold increase in mean rivaroxaban AUC and a 1.3-fold increase in mean C_{max}. This increase is within the magnitude of the normal variability of AUC and C_{max} and is considered as clinically not relevant (*see section 'Pharmacokinetic properties'*).

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. The concomitant use of INVAROX with other strong CYP 3A4 inducers (e.g., phenytoin, carbamazepine, phenobarbitone or St. John's Wort) may also lead to a decreased rivaroxaban plasma concentration.

Strong CYP 3A4 inducers should be used with caution in ACS, or CAD or PAD patients treated with 2.5 mg INVAROX twice daily.

4.5.2 Pharmacodynamic interactions

After combined administration of enoxaparin (40 mg single dose) with rivaroxaban (10 mg single dose), an additive effect on anti factor Xa activity was observed without any additional effects on clotting tests (PT, aPTT). Enoxaparin did not affect the pharmacokinetics of rivaroxaban (*see section 'Special Warnings and Precautions for Use'*).

Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) did not show a pharmacokinetic interaction (with rivaroxaban 15 mg) but a relevant increase in bleeding times was observed in a subset of patients which was not correlated to platelet aggregation, P-selectin or GPIIb / IIIa receptor levels (*see section 'Special Warnings and Precautions for Use'*).

No clinically relevant prolongation of bleeding time was observed after concomitant administration of rivaroxaban (15 mg) and 500 mg naproxen. Nevertheless there may be individuals with more pronounced pharmacodynamic response (*see section 'Special Warnings*

and Precautions for Use').

Converting patients from 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. From day 4 after stopping warfarin onwards, all tests (including PT, aPTT, inhibition of Factor Xa activity and ETP) reflected only the effect of rivaroxaban (*see section 'Dosage and Method of Administration')*.

If it is desired to test the pharmacodynamic effects of warfarin during the conversion period, INR measurement can be used at the Ctrough 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.

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

4.5.3 Food and dairy products

2.5 mg INVAROX can be taken with or without food (*see section 'Pharmacokinetic Properties'*).

4.5.4 Interactions shown not to exist

There were no mutual pharmacokinetic interactions between rivaroxaban 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 aluminum hydroxide / magnesium hydroxide, naproxen, clopidogrel or enoxaparin did not affect rivaroxaban bioavailability and pharmacokinetics.

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

4.5.5 Interactions with laboratory parameters

Clotting parameter tests (PT, aPTT, HepTest®) are affected as expected by the mode of action of INVAROX *(see section 'Pharmacodynamic properties')*.

4.6 Pregnancy and lactation

4.6.1 Women of childbearing potential / Contraception

INVAROX should be used in women of childbearing potential only with effective contraception.

4.6.2 Pregnancy

Safety and efficacy of INVAROX 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., hemorrhagic complications) leading to reproductive toxicity (*see section 'Preclinical safety data'*). No primary teratogenic potential was identified. Due to the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, INVAROX is contraindicated in pregnancy (*see section 'Contraindications', 'Preclinical Safety Data'*).

4.6.3 Lactation

Safety and efficacy of INVAROX have not been established in nursing mothers. In rats rivaroxaban is secreted into breast milk.
Therefore INVAROX may only be administered after breastfeeding is discontinued (*see section 'Contraindications', 'Preclinical Safety Data'*).

4.7 Effects on ability to drive or use machines

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

4.8 Undesirable effects

4.8.1 Summary of the safety profile

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

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

Indication	Number of patients*	Maximum daily dose	Maximum treatment duration
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	6,097	10 mg	39 days
Prevention of venous thromboembolism in medically ill patients	3,997	10 mg	39 days
Treatment of DVT, PE and prevention of recurrent DVT, PE	6,790	Day 1 - 21: 30 mg Day 22 and onwards: 20 mg After at least six months: 10 mg or 20 mg	21 months
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	7,750	20 mg	41 months

Prevention of cardiovascular death in patients after an ACS	10,225	5 mg or 10 mg respectively, in combination with either ASA or ASA plus clopidogrel or ticlopidine	31 months
To reduce the risk of major cardiovascular events (CV death, MI and stroke) in patients with CAD or PAD	18,244	5mg in combination with 100mg ASA or 10mg alone	47 months

*Patients exposed to at least one dose of rivaroxaban

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

Indication	**Any Bleeding**	**Anemia**
Prevention of venous thromboembolism (VTE) in adult patients undergoing elective hip or knee replacement surgery	6.8% of patients	5.9% of patients
Prevention of venous thromboembolism in medically ill patients	12.6% of patients	2.1% of patients
Treatment of DVT, PE and prevention of recurrent DVT, PE	23% of patients	1.6% of patients
Prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation	28 per 100 patient years	2.5 per 100 patient years
Prevention of cardiovascular death in patients after an ACS	22 per 100 patient years	1.4 per 100 patient years
To reduce the risk of major cardiovascular events (CV death, MI and stroke) in patients with CAD or PAD	6.7 per 100 patient years	0.15 per 100 patient years*

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

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

Hemorrhagic complications may present as weakness, paleness, dizziness, headache or unexplained swelling, dyspnea, and unexplained shock. In some cases as a consequence of anemia, symptoms of cardiac ischemia like chest pain or angina pectoris have been observed.

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

4.8.2 Tabulated list of adverse reactions

The frequencies of ADRs reported with rivaroxaban are summarized in the table below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Frequencies are defined as:

very common (≥ 1/10), common
(≥ 1/100 to < 1/10),
uncommon (≥ 1/1,000 to < 1/100),
rare (≥ 1/10,000 to < 1/1,000),

Table 2: All treatment-emergent adverse drug reactions reported in patients in phase III studies (pooled RECORD 1-4, ROCKET, J-ROCKET, MAGELLAN, ATLAS EINSTEIN (DVT/PE/Extension/CHOICE), and COMPASS*)

System Organ Class (MedDRA)	Common	Uncommon	Rare
Blood and the lymphatic system disorders	Anemia (incl. respective laboratory parameters)	Thrombocytosis (incl. platelet count increased) [A]	
Cardiac disorders		Tachycardia	
Eye disorders	Eye hemorrhage (incl. conjunctival hemorrhage)		

Gastrointestinal disorders	Gingival bleeding Gastrointestinal tract hemorrhage (incl. rectal hemorrhage) Gastrointestinal and abdominal pains Dyspepsia Nausea Constipation [A] Diarrhea Vomiting [A]	Dry mouth	
General disorders and administration site conditions	Fever [A] Edema peripheral Decreased general strength and energy (incl. fatigue and asthenia)	Feeling unwell (incl. malaise)	Localized edema [A]

Table 2: All treatment-emergent adverse drug reactions reported in patients in phase III studies (pooled RECORD 1-4, ROCKET, J-ROCKET, MAGELLAN, ATLAS EINSTEIN (DVT/PE/Extension/CHOICE), and COMPASS*)

System Organ Class (MedDRA)	Common	Uncommon	Rare
Hepato-biliary disorders		Hepatic impairment	Jaundice
Immune system disorders		Allergic reaction Dermatitis allergic	
Injury, poisoning and postprocedural complications	Postprocedural hemorrhage (incl. postoperative anemia and wound hemorrhage) Contusion	Wound secretion [A]	vascular pseudoaneurysm [C]
Investigations	Increase in transaminases	Increase in bilirubin Increase in blood alkaline phosphatase [A] Increase in LDH [A] Increase in lipase [A] Increase in amylase [A] Increase in GGT [A]	Bilirubin conjugated increased (with or without concomitant increase of ALT)
Musculoskeletal, connective tissue and bone disorders	Pain in extremity [A]	Hemarthrosis	Muscle hemorrhage
Nervous system disorders	Dizziness Headache	Cerebral and intracranial hemorrhage Syncope	
Renal and urinary disorders	Urogenital tract hemorrhage (incl. hematuria and menorrhagia [B]) Renal impairment (incl. blood creatinine increased, blood urea increased) [A]		

Table 2: All treatment-emergent adverse drug reactions reported in patients in phase III studies (pooled RECORD 1-4, ROCKET, J-ROCKET, MAGELLAN, ATLAS EINSTEIN (DVT/PE/Extension/CHOICE), and COMPASS*)

System Organ Class (MedDRA)	Common	Uncommon	Rare
Respiratory tract disorders	Epistaxis Hemoptysis		
Skin and subcutaneous tissue disorders	Pruritus (incl. uncommon cases of generalized pruritus) Rash Ecchymosis Cutaneous and subcutaneous hemorrhage	Urticaria	
Vascular disorders	Hypotension Hematoma		

[A] observed in prevention of venous thromboembolism (VTE) in adult patients undergoing total hip replacement or total knee replacement surgery.

[B] observed in treatment of DVT, PE and prevention of recurrence as very common in women < 55 years

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

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

< ADR term representation is based on MedDRA version 20.0 >

4.8.2.1 Post marketing observations

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

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

Hepatobiliary disorders: Cholestasis, Hepatitis (incl. hepatocellular injury) (In the pooled phase III trials, these events were rare (≥ 1/10,000 to < 1/1,000))

Blood and lymphatic system disorders: Thrombocytopenia (In the pooled phase III trials, these events were uncommon (≥ 1/1,000 to < 1/100)); agranulocytosis

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

Skin and subcutaneous tissue disorders: Stevens-Johnson syndrome

4.9 Overdose

Rare cases of overdose up to 600 mg have been reported without bleeding complications or other adverse reactions. Due to limited absorption a ceiling effect with no further increase in average plasma exposure is expected at supratherapeutic doses of 50 mg or above.

A specific antidote antagonizing the pharmacodynamic effect of rivaroxaban is not available. The use of activated charcoal to reduce absorption in case of INVAROX overdose may be considered. Due to the high plasma protein binding rivaroxaban is not expected to be dialyzable.

4.9.1 Management of Bleeding

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

If bleeding cannot be controlled by the above measures, administration of a specific procoagulant reversal agent should be considered, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC), or recombinant factor VIIa (r- FVIIa). However, there is currently very limited clinical experience with the use of these products in individuals receiving rivaroxaban *(see section 'Pharmacodynamic properties').*

Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban.

There is limited experience with tranexamic acid and no experience with aminocaproic acid and aprotinin) in individuals receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with the systemic hemostatics desmopressin in individuals receiving rivaroxaban.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Direct factor Xa inhibitors

ATC Code: B01AF01

5.1.1 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.

5.1.2 Pharmacodynamic effects

Dose-dependent inhibition of factor Xa activity was observed in humans. Prothrombin time (PT) is influenced by rivaroxaban in a dose dependent way with a close correlation to plasma concentrations (r value equals 0.98) if Neoplastin is used for the assay. Other reagents would provide different results. The readout for PT is to be done in seconds, because the INR (International Normalized Ratio) is only calibrated and validated for coumarins and cannot be used for any other anticoagulant. In patients undergoing major orthopedic surgery, the 5/95 percentiles for PT (Neoplastin) 2-4 hours after tablet intake (i.e. at the time of maximum effect) ranged from 13 to 25 sec.

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

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

There is no need for monitoring of coagulation parameters during routine clinical treatment with INVAROX. However, if clinically indicated, rivaroxaban concentrations can be measured by calibrated quantitative anti-Factor Xa tests (*see section 'Pharmacokinetic properties'*).

5.1.3 ACS: Clinical efficacy and safety

The rivaroxaban clinical program was designed to demonstrate the efficacy of rivaroxaban for the prevention of cardiovascular (CV) death, MI or stroke in subjects with a recent ACS (ST- elevation myocardial infarction [STEMI], non- ST-elevation myocardial infarction [NSTEMI] or unstable angina [UA]). In the pivotal double-blind ATLAS ACS 2 TIMI 51 trial, 15,526 patients were randomly assigned in a 1:1:1 fashion to one of three treatment groups: Rivaroxaban 2.5 mg orally twice daily, 5 mg orally twice daily or to placebo twice daily. co-administered with ASA alone or with ASA plus a thienopyridine (clopidogrel or ticlopidine). Patients with an ACS under the age of 55 had to have either diabetes mellitus or a previous MI. The median time on treatment was 13 months and overall treatment duration was up to almost 3 years. 93.2 % of patients received ASA concomitantly plus thienopyridine treatment and 6.8 % ASA only. Among patients receiving dual anti-platelets therapy 98.8% received clopidogrel, 0.9 % received ticlopidine and 0.3 % received

prasugrel. Patients received the first dose of rivaroxaban at a minimum of 24 hours and up to 7 days (mean 4.7 days) after admission to the hospital, but as soon as possible after stabilisation of the ACS event, including revascularisation procedures and when parenteral anticoagulation therapy would normally be discontinued.

Both the 2.5 mg twice daily and the 5 mg twice daily regimens of rivaroxaban were effective in further reducing the incidence of CV events on a background of standard antiplatelet care. The 2.5 mg twice daily regimen reduced mortality, and there is evidence that the lower dose had lower bleeding risks, therefore rivaroxaban 2.5 mg twice daily co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine is recommended for the prevention of cardiovascular death in adult patients after an ACS with elevated cardiac biomarkers.

Relative to placebo, rivaroxaban significantly reduced the primary composite endpoint of CV death, MI, or stroke. The benefit was driven by a reduction in CV death and MI and appeared early with a constant treatment effect over the entire treatment period (see Table 3 and Figure 1). Also the first secondary endpoint (all cause death, MI or stroke) was reduced significantly. An additional retrospective analysis showed a nominally significant reduction in the incidence rates of stent thrombosis compared with placebo (see Table 3). The incidence rates for the principal safety outcome (non-CABG TIMI major bleeding events) were higher in patients treated with rivaroxaban than in patients who received placebo (see Table 5). However the incidence rates were balanced between rivaroxaban and placebo for the components of fatal bleeding events, hypotension requiring treatment with intravenous inotropic agents and surgical intervention for ongoing bleeding.

In Table 4 the efficacy results of patients undergoing percutaneous coronary intervention (PCI) are presented. The safety results in this subgroup of patients undergoing PCI were comparable to the overall safety results.

Table 3: Efficacy results from phase III ATLAS ACS 2 TIMI 51

Study Population	**Patients with a recent acute coronary syndrome[a]**	
Treatment Dosage	Rivaroxaban 2.5mg, twice daily, N=5, 114 n(%) Hazard Ratio (95% CI) p-value[b]	Placebo N=5,113 n(%)
Cardivascular death, MI or stroke	313 (6.1%) 0.84 (0.72, 0.97) p=0.020*	376 (7.4%)
All-cause death, MI or stroke	320 (6.3%) 0.83 (0.72, 0.97) p=0.016*	386 (7.5%)

Cardiovascular death	94 (1.8%) 0.66 (0.51, 0.86) p=0.002**	143 (2.8%)
All-cause death	103 (2.0%) 0.68 (0.53, 0.87) p=0.002**	153 (3.0%)
MI	205 (4.0%) 0.90 (0.75, 1.09) p=0.270	229 (4.5%)
Stroke	46 (0.9%) 1.13 (0.74, 1.73) p=0.562	41 (0.8%)
Stent thrombosis	61 (1.2%) 0.70 (0.51, 0.97) p=0.033**	87 (1.7%)

[a] modified intent to treat analysis set (intent to treat total analysis set for stent thrombosis)

[b] vs. placebo; Log-Rank p-value

* statistically superior

** nominally significant

Table 4: Efficacy results from phase III ATLAS ACS 2 TIMI 51 in patients undergoing PCI

Study Population	**Patients with a recent acute coronary syndrome undergoing PCI[a]**	
Treatment Dosage	Rivaroxaban 2.5mg, twice daily, N=3114 n(%) Hazard Ratio (95% CI) p-value[b]	Placebo N=3096 n(%)
Cardivascular death, MI or stroke	153 (4.9%) 0.94 (0.75, 1.17) p=0.572	165 (5.3%)
All-cause death, MI or stroke	24 (0.8 %) 0.54 (0.33, 0.89) p = 0.013**	45 (1.5 %)
Cardiovascular death	24 (0.8 %)	45 (1.5 %)

	0.54 (0.33, 0.89) p = 0.013**	
All-cause death	31 (1.0 %) 0.64 (0.41, 1.01) p = 0.053	49 (1.6 %)
MI	115 (3.7 %) 1.03 (0.79, 1.33) p = 0.829	113 (3.6 %)
Stroke	27 (0.9 %) 1.30 (0.74, 2.31) p = 0.360	21 (0.7 %)
Stent thrombosis	47 (1.5 %) 0.66 (0.46, 0.95) p = 0.026**	71 (2.3 %)

[a] modified intent to treat analysis set (intent to treat total analysis set for stent thrombosis)
[b] vs. placebo; Log-Rank p-value

** nominally significant

Table 5: Safety results from phase III ATLAS ACS 2 TIMI 51

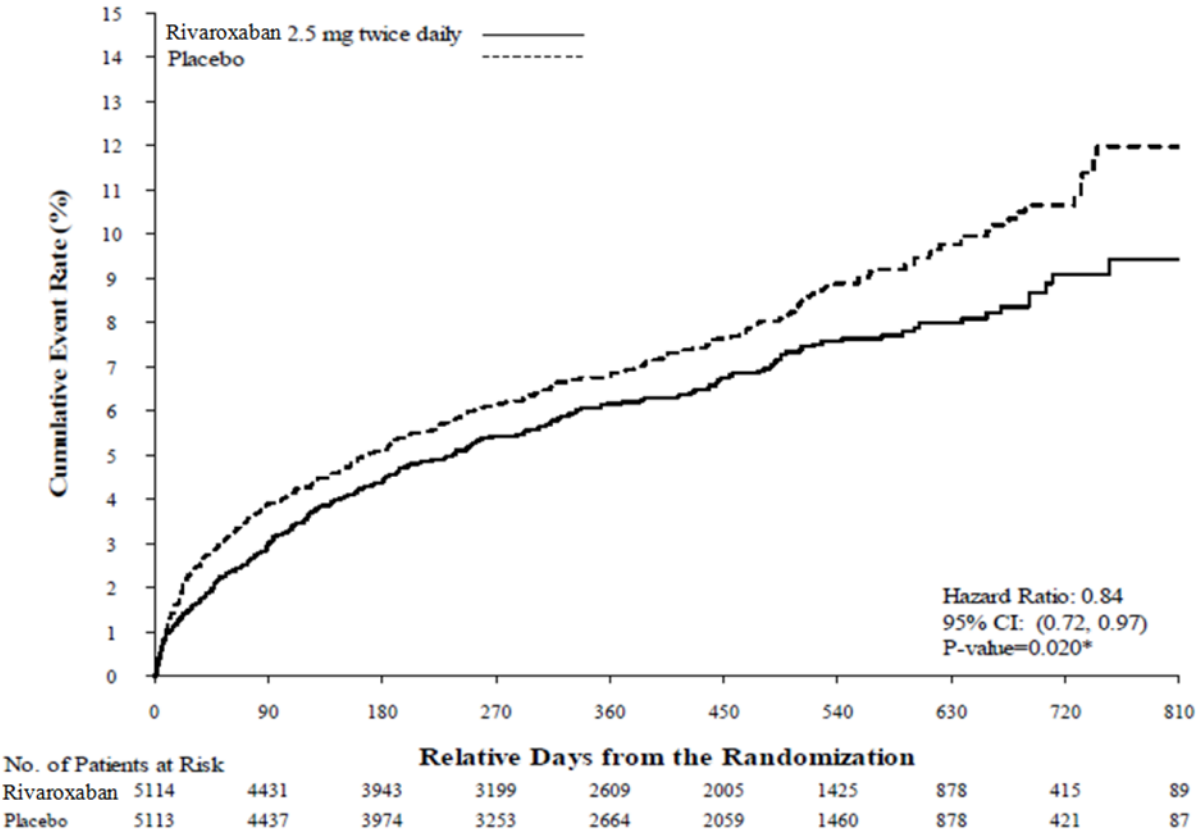
Study Population	**Patients with a recent acute coronary[a]**	
Treatment Dosage	Rivaroxaban 2.5mg, twice daily, N=5,115 n(%) Hazard Ratio (95% CI) p-value[b]	Placebo N=5,125 n(%)
Non-CABG TIMI major bleeding event	65 (1.3 %) 3.46 (2.08, 5.77) p = < 0.001*	19 (0.4 %)
Fatal bleeding event	6 (0.1 %) 0.67 (0.24, 1.89) p = 0.450	9 (0.2 %)
Symptomatic intracranial haemorrhage	14 (0.3 %) 2.83 (1.02, 7.86) p = 0.037	5 (0.1 %)
Hypotension requiring treatment with intravenous inotropic agents	3 (0.1 %)	3 (0.1 %)
Surgical intervention for ongoing bleeding	7 (0.1 %)	9 (0.2 %)

Transfusion of 4 or more units of blood over a 48 hour period	19 (0.4 %)	6 (0.1 %)

[a] treatment-emergent safety analysis set
[b] vs. placebo; Log-Rank p-value

* statistically significant

Figure 1: Time to First Occurrence of Primary Efficacy Endpoint (CV death, MI or stroke)



A nominally significant reduction of the primary composite endpoint of CV death, MI or stroke was shown in patients with elevated biomarkers (troponin or CK-MB) and without a prior stoke/TIA in a retrospective analysis, relative to placebo. The benefit was driven by a reduction in CV death and MI and appeared early with a constant treatment effect over the entire treatment period (see Table 6 and Figure 1). The incidence rates for the principal safety outcome (non-CABG TIMI major bleeding events) in this population were higher in patients treated with rivaroxaban than in patients who received placebo. However as for the overall trial population the incidence rates were balanced between rivaroxaban and placebo for the components of fatal bleeding events, hypotension requiring treatment with intravenous inotropic agents and surgical intervention for ongoing bleeding (see Table 7).

Table 6: Efficacy results from phase III ATLAS ACS 2 TIMI 51 in patients with elevated biomarkers (troponin or CK-MB) and without a prior stoke/TIA

Study Population	Patients with recent acute coronary syndrome with elevated biomarkers (troponin or CK-MB) and without a prior stoke/TIA a)	
Treatment Dosage	Rivaroxaban 2.5 mg, twice daily, N=4,104 n (%) Hazard Ratio (95 % CI) p-value b)	Placebo N=4,160 n (%)
Cardiovascular death, MI or stroke	256 (6.2 %) 0.80 (0.68, 0.94) p = 0.007**	327 (7.9 %)
All-cause death, MI or stroke	263 (6.4 %) 0.80 (0.68, 0.94) p = 0.007**	335 (8.1 %)
Cardiovascular death	68 (1.7 %) 0.55 (0.41, 0.74) p = < 0.001**	127 (3.1 %)
All-cause death	77 (1.9 %) 0.58 (0.44, 0.77) p = < 0.001**	135 (3.2 %)
MI	176 (4.3 %) 0.88 (0.72, 1.08) p = 0.215	204 (4.9 %)
Stroke	35 (0.9 %) 1.23 (0.75, 2.02) p = 0.403	29 (0.7 %)
Stent thrombosis	54 (1.3 %) 0.69 (0.49, 0.98) p = 0.036**	79 (1.9 %)

a) modified intent to treat analysis set (intent to treat total analysis set for stent thrombosis)

b) vs. placebo; Log-Rank p-value

** nominally significant

Table 7: Safety results from phase III ATLAS ACS 2 TIMI 51 in patients with elevated biomarkers (troponin or CK-MB) and without a prior stoke/TIA

Study Population	**Patients with recent acute coronary syndrome with elevated biomarkers (troponin or CK-MB) and without a prior stoke/TIA a)**	
Treatment Dosage	Rivaroxaban 2.5 mg, twice daily, N=4,096 n (%) Hazard Ratio (95 % CI) p-value b)	Placebo N=4,157 n (%)
Non-CABG TIMI major bleeding event	54 (1.3 %) 3.44 (1.97, 6.01) p = < 0.001**	16 (0.4 %)
Fatal bleeding event	3 (<0.1 %) 0.38 (0.10, 1.45) p = 0.143	8 (0.2 %)
Symptomatic intracranial haemorrhage	10 (0.2 %) 2.54 (0.80, 8.11) p = 0.102	4 (<0.1 %)
Hypotension requiring treatment with intravenous inotropic agents	3 (<0.1 %)	3 (<0.1 %)
Surgical intervention for ongoing bleeding	6 (0.1 %)	7 (0.2 %)
Transfusion of 4 or more units of blood over a 48 hour period	16 (0.4 %)	5 (0.1 %)

a) treatment-emergent safety analysis set

b) vs. placebo; Log-Rank p-value

** nominally significant

5.1.4 CAD or PAD: Clinical efficacy and safety

The rivaroxaban clinical program was designed to demonstrate the efficacy and safety of rivaroxaban for the prevention of stroke, myocardial infarction, or cardiovascular death in patients with CAD or PAD. In the pivotal phase III double-blind COMPASS trial, 27,395 patients were randomly assigned to one of three antithrombotic treatment groups: Rivaroxaban 2.5 mg twice

daily in combination with ASA 100 mg once daily, rivaroxaban 5 mg twice daily or to ASA 100 mg once daily in a 1:1:1 fashion.

Patients with established CAD or PAD were eligible. Patients with CAD who were younger than 65 years of age were also required to have documentation of atherosclerosis involving at least two vascular beds or to have at least two additional cardiovascular risk factors (current smoking, diabetes mellitus, an estimated glomerular filtration rate [eGFR] <60 ml per minute, heart failure, or non-lacunar ischemic stroke ≥1 month earlier). Certain patients were excluded, such as those patients in need of dual antiplatelet, other non-ASA antiplatelet, or oral anticoagulant therapies, as well as patients with a history of ischemic, non-lacunar stroke within 1 month, any history of hemorrhagic or lacunar stroke, or patients with eGFR < 15 ml/min.

The mean duration of follow-up was 23 months and the maximum follow-up was 3.9 years. The mean age was 68 years and 21% of the subject population were ≥75 years. Of the patients included, 91% had CAD, 27% had PAD, and 18% had both CAD and PAD. Of the patients with CAD, 69% had prior myocardial infarction, 60% had prior percutaneous transluminal coronary angioplasty (PTCA)/atherectomy/percutaneous coronary intervention (PCI), and 26% had a history of coronary artery bypass grafting (CABG) prior to study. Of the patients with PAD, 49% had intermittent claudication, 27% had peripheral artery bypass surgery or peripheral percutaneous transluminal angioplasty (PTA), 26% had asymptomatic carotid artery stenosis >50%, and 5% had limb or foot amputation for arterial vascular disease.

Relative to ASA 100 mg, rivaroxaban 2.5 mg twice daily in combination with ASA 100 mg once daily was superior in the reduction of the primary composite outcome of stroke, myocardial infarction or cardiovascular death. The benefit was observed early with a constant treatment effect over the entire treatment period (see Table 8 and Figure 2). The composite secondary outcomes (composites of coronary heart disease death, or cardiovascular death, with myocardial infarction, ischemic stroke, and acute limb ischemia) as well as all-cause mortality were reduced (see Table 8). Acute limb ischemic events were reduced (hazard ratio [HR] 0.55; 95% confidence interval [CI] 0.32-0.92). Amputations for cardiovascular reasons were also reduced (HR 0.48; 95% CI 0.26-0.89). The composite outcome of stroke, myocardial infarction and all-cause mortality was also reduced (HR 0.79; 95% CI 0.70-0.88; p=0.00005, post-hoc analysis). There was a significant 1.7-fold increase of the primary safety outcome (modified International Society on Thrombosis and Haemostasis [ISTH] major bleeding events) in patients treated with rivaroxaban 2.5 mg twice daily in combination with ASA 100 mg once daily compared to patients who received ASA 100 mg (see Table 10). However the incidence rates for fatal bleeding events, non-fatal symptomatic bleeding into a critical organ as well as intracranial bleeding events did not differ significantly. The prespecified composite outcome for net clinical benefit (cardiovascular death, myocardial infarction, stroke, fatal or symptomatic critical-organ bleeding events) was reduced (see Table 8). The results in patients with PAD, CAD, and both CAD and PAD were consistent with the overall efficacy and safety results (Table 9).

In the 3.8% of patients with a history of ischemic, non-lacunar stroke (median time since stroke: 5 years), the reduction of stroke, myocardial infarction, cardiovascular death, and the

increase of major bleeding (net clinical benefit HR 0.64; 95% CI 0.4-1.0) were consistent with the overall population (*see section 'Special warnings and precautions for use'*).

Relative to ASA 100 mg, rivaroxaban 5 mg twice daily alone did not significantly reduce the primary composite efficacy outcome of stroke, myocardial infarction or cardiovascular death (HR 0.90; 95% CI 0.79-1.03; p = 0.11490). The incidence rates for the primary safety outcome (modified ISTH major bleeding events) were significantly increased in patients treated with rivaroxaban 5 mg twice daily compared with patients who received ASA 100 mg once daily (HR 1.51; 95% CI 1.25-1.84; p = 0.00003).

Table 8: Efficacy results from phase III COMPASS

Study Population	**Patients with CAD or PAD** [a)]		
Treatment Dosage	**Rivaroxaban 2.5 mg bid in combination with ASA 100 mg od, N=9152 n (Cum. risk %)**[b)]	**ASA 100 mg od N=9126 n (Cum. risk %)**[b)]	**Hazard Ratio (95 % CI) p-value** [c)]
Stroke, MI, CV death	379 (5.2%)	496 (7.2%)	0.76 (0.66;0.86) p = 0.00004*
- Stroke	83 (1.2%)	142 (2.2%)	0.58 (0.44;0.76) p = 0.00006
- MI	178 (2.5%)	205 (2.9%)	0.86 (0.70;1.05) p = 0.14458
- CV death	160 (2.2%)	203 (2.9%)	0.78 (0.64;0.96) p = 0.02053
Coronary heart disease death, MI, ischemic stroke, acute limb ischemia	329 (4.5%)	450 (6.6%)	0.72 (0.63;0.83) p = 0.00001
- Coronary heart disease death#	86 (1.2%)	117 (1.6%)	0.73 (0.55;0.96) p = 0.02611
- Ischemic stroke	64 (0.9%)	125 (2.0%)	0.51 (0.38;0.69) p = 0.00001
- Acute limb ischemia**	22 (0.3%)	40 (0.6%)	0.55 (0.32;0.92) p = 0.02093
CV death, MI,	389 (5.3%)	516 (7.5%)	0.74 (0.65;0.85)

ischemic stroke, acute limb ischemia			p = 0.00001
All-cause mortality	313 (4.5%)	378 (5.6%)	0.82 (0.71;0.96) p = 0.01062
Stroke, MI, all-cause mortality	526 (7.4%)	659 (9.6%)	0.79 (0.70;0.88) p=0.00005
CV death, MI, stroke, fatal or symptomatic critical-organ bleeding events (net clinical benefit)	431 (5.9%)	534 (7.7%)	0.80 (0.70;0.91) p=0.00052

a) intention to treat analysis set, primary analyses

b) Cum. Risk: Cumulative incidence risk (Kaplan-Meier estimates) at 30 months

c) vs. ASA 100 mg; Log-Rank p-value

* The reduction in the primary efficacy outcome was statistically superior.

Nominal p-value significant at $p<0.05$.

CHD coronary heart disease death: death due to acute MI, sudden cardiac death, or CV procedure

** Acute limb ischemia is defined as limb-threatening ischemia leading to an acute vascular intervention (i.e., pharmacologic, peripheral arterial surgery/reconstruction, peripheral angioplasty/stent, or amputation)

bid: twice daily; od: once daily; CI: confidence interval; MI: myocardial infarction; CV: cardiovascular

Table 9: Efficacy and safety results from phase III COMPASS in subpopulation with CAD, PAD, or both CAD and PAD

Study Population	**Patients with CAD or PAD by subgroups [a)]**		
Treatment Dosage	**Rivaroxaban 2.5 mg bid in combination with ASA 100 mg od, N=9152 n (Cum. risk %)[b)]**	**ASA 100 mg od N=9126 n (Cum. risk %)[b)]**	**Hazard Ratio (95 % CI) p-value [c)]**
Patients with PAD	**N=2492 (100%)[d)]**	**N=2504 (100%)[d)]**	
Stroke, MI, or CV death	126 (6.6%)	174 (10.3%)	0.72 (0.57;0.90) p = 0.00466
Modified ISTH major bleeding	77 (4.0%)	48 (2.5%)	1.61 (1.12;2.31) p = 0.00890
Stroke MI, CV death, fatal or symptomatic critical organ	140 (7.1%)	185 (10.7%)	0.75 (0.60;0.94) p = 0.01072

bleeding			
Patients with CAD	**N=8313 (100%)[d)]**	**N=8261 (100%)[d)]**	
Stroke, MI, or CV death	347 (5.2%)	460 (7.3%)	0.74 (0.65;0.86) p = 0.00003
Modified ISTH major bleeding	263 (4.0%)	158 (2.5%)	1.66 (1.37;2.03) p < 0.00001
Stroke, MI, CV death, fatal or symptomatic critical organ bleeding	392 (5.8%)	494 (7.8%)	0.78 (0.69;0.90) p = 0.00032
Patients with CAD and PAD	**N=1656 (100%)**	**N=1641 (100%)**	
Stroke, MI, or CV death	94 (7.2%)	138 (12.0%)	0.67 (0.52;0.87) p = 0.00262
Modified ISTH major bleeding	52 (4.3%)	36 (2.6%)	1.43 (0.93;2.19) p = 0.09819
Stroke, MI, CV death, fatal or symptomatic critical organ bleeding	101 (7.5%)	145 (12.3%)	0.68 (0.53;0.88) p = 0.00327

a) intention to treat analysis set, primary analyses

b) Cum. Risk: Cumulative incidence risk (Kaplan-Meier estimates) at 30 months

c) vs. ASA 100 mg; Log-Rank p-value

d) Patients could have more than one clinical diagnosis indicating either CAD and/or PAD.

bid: twice daily; od: once daily; CI: confidence interval; MI: myocardial infarction, CV: cardiovascular

Table 10: Safety results from phase III COMPASS

Study Population	**Patients with CAD or PAD [a)]**		
Treatment Dosage	**Rivaroxaban 2.5 mg bid in combination with ASA 100 mg od, N=9152 n (Cum. risk %)[b)]**	**ASA 100 mg od N=9126 n (Cum.risk %)[b)]**	**Hazard Ratio (95 % CI) p-value [c)]**
Modified ISTH major bleeding	288 (3.9%)	170 (2.5%)	1.70 (1.40;2.05) p < 0.00001
- Fatal bleeding event	15 (0.2%)	10 (0.2%)	1.49 (0.67;3.33) p = 0.32164

- Symptomatic bleeding in critical organ (non-fatal)	63 (0.9%)	49 (0.7%)	1.28 (0.88;1.86) p = 0.19679
- Bleeding into the surgical site requiring reoperation (non-fatal, not in critical organ)	10 (0.1%)	8 (0.1%)	1.24 (0.49;3.14) p = 0.65119
- Bleeding leading to hospitalization (non-fatal, not in critical organ, not requiring reoperation)	208 (2.9%)	109 (1.6%)	1.91 (1.51;2.41) p<0.00001
- With overnight stay	172 (2.3%)	90 (1.3%)	1.91 (1.48;2.46) p<0.00001
- Without overnight stay	36 (0.5%)	21 (0.3%)	1.70 (0.99;2.92) p=0.04983
Major gastrointestinal bleeding	140 (2.0%)	65 (1.1%)	2.15 (1.60;2.89) p < 0.00001
Major intracranial bleeding	28 (0.4%)	24 (0.3%)	1.16 (0.67;2.00) p = 0.59858

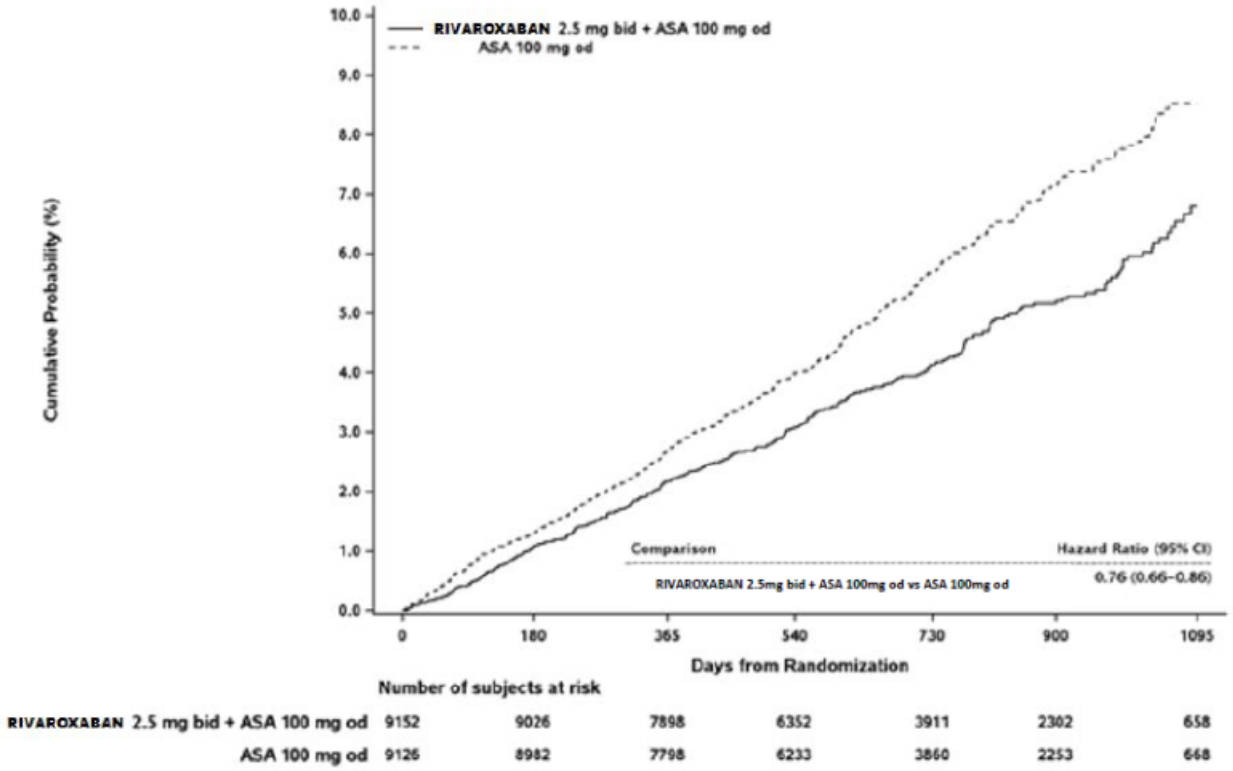
a) intention-to-treat analysis set, primary analyses

b) Cum. Risk: Cumulative incidence risk (Kaplan-Meier estimates) at 30 months

c) vs. ASA 100 mg; Log-Rank p-value

bid: twice daily; od: once daily; CI: confidence interval;

Figure 2: Time to first occurrence of primary efficacy outcome (stroke, myocardial infarction, cardiovascular death) in COMPASS



bid: twice daily; od: once daily; CI: confidence interval

Patients with high risk triple positive antiphospholipid syndrome

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

5.2 Pharmacokinetic properties

5.2.1 Absorption and Bioavailability

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

Oral absorption of rivaroxaban is almost complete and oral bioavailability is high (80-100%) for the 2.5 mg and 10 mg tablet dose, irrespective of fasting/fed conditions. Intake with food does not affect rivaroxaban AUC or C_{max} at the 10 mg dose. INVAROX 2.5 mg tablets and 10 mg tablets can be taken with or without food (*see section 'Dosage and Method of Administration'*).

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

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

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

5.2.2 Distribution

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

5.2.3 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 fecal 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 metabolized 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 low-clearance drug. Elimination of rivaroxaban from plasma occurred with terminal half-lives of 5 to 9 hours in young individuals, and with terminal half- lives of 11 to 13 hours in the elderly.

5.2.4 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 'Dosage and Method of Administration'*).

5.2.5 Gender

There were no clinically relevant differences in pharmacokinetics between male and female patients (*see section 'Dosage and Method of Administration'*).

5.2.6 Body weight

Extremes in body weight (<50 kg vs >120 kg) had only a small influence on rivaroxaban plasma concentrations (less than 25%) (*see section 'Dosage and Method of Administration'*).

5.2.7 Children and adolescents

Safety and efficacy have not been established for children and adolescents below 18 years (*see section 'Dosage and Method of Administration'*).

5.2.8 Ethnic differences

No clinically relevant interethnic differences among Caucasian, African-American, Hispanic, Japanese or Chinese patients were observed regarding pharmacokinetics and pharmacodynamics (*see section 'Dosage and Method of Administration'*).

5.2.9 Hepatic impairment

The effect of hepatic impairment on rivaroxaban pharmacokinetics has been studied in subjects categorized according to the Child Pugh classification, a standard procedure in clinical development. The Child Pugh classification's original purpose is to assess the prognosis of chronic liver disease, mainly cirrhosis. 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. The decision to treat patients with an anticoagulant should therefore be made independently of the Child Pugh classification.
INVAROX is contraindicated in patients with hepatic disease which is associated with coagulopathy leading to a clinically relevant bleeding risk.

Cirrhotic patients with mild hepatic impairment (classified as Child Pugh A) exhibited only minor changes in rivaroxaban pharmacokinetics (1.2-fold increase in rivaroxaban AUC on average), nearly comparable to their matched healthy control group. No relevant difference in pharmacodynamic properties was observed between these groups.

In cirrhotic patients with moderate hepatic impairment (classified as Child Pugh B), rivaroxaban mean AUC was significantly increased by 2.3-fold compared to healthy volunteers, due to significantly impaired drug clearance which indicates significant liver disease. Unbound AUC was increased 2.6-fold. 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 and I which are synthesized 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 'Dosage and Method of Administration', 'Contraindications'*).

5.2.10 Renal impairment

There was an increase in rivaroxaban exposure being inversely correlated to the decrease in renal function, as assessed via creatinine clearance measurements.
In individuals with mild (CrC: 80-50 mL/min), moderate (CrC: <50-30 mL/min) or severe (CrC: <30-15 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 'Dosage and Method of Administration', 'Special Warnings and Precautions for Use'*).

Corresponding increases in pharmacodynamic effects were more pronounced (*see section 'Dosage and Method of Administration', 'Special Warnings and Precautions for Use'*).

In individuals with mild, moderate or severe renal impairment the overall inhibition of factor Xa activity was increased by a factor of 1.5, 1.9 and 2.0 respectively as compared to healthy volunteers; prolongation of PT was similarly increased by a factor of 1.3, 2.2 and 2.4 respectively.
There are no data in patients with CrC <15 mL/min.

Use is not recommended in patients with creatinine clearance <15 mL/min. INVAROX is to be used with caution in patients with severe renal impairment creatinine clearance 15-30 mL/min (*see section 'Dosage and Method of Administration', 'Special Warnings and Precautions for Use'*).

Due to the underlying disease patients with severe renal impairment are at an increased risk of both bleeding and thrombosis.

5.2.11 Concomitant administration of strong CYP 3A4 inducers

In a phase I trial, co-administration of rivaroxaban with the strong CYP 3A4 and P-gp inducer rifampicin led to an approximate 50% decrease in mean rivaroxaban AUC, with parallel decreases in its pharmacodynamic effects (*see section 'Interaction with other medicinal products and other forms of interaction'*).

In a phase IIa trial, the PK/PD of an adapted rivaroxaban dosing regimen (30 mg twice daily in the first 3 weeks of treatment, followed by 20 mg twice daily) has been studied in 19 patients treated for DVT or PE and who concomitantly were medicated with a strong CYP 3A4 and P-gp inducer (rifampicin or phenytoin). The adapted dosing regimen in these patients led to a similar exposure and pharmacodynamics when compared to patients treated for DVT (15 mg twice daily in the first 3 weeks of treatment, followed by 20 mg once daily) without the concomitant administration of a strong CYP 3A4 inducer.

5.3 Preclinical safety data

The non-clinical safety evaluation in the data from conventional and appropriate studies of safety pharmacology, single and repeat-dose toxicity, genotoxicity, phototoxicity, and carcinogenicity and toxicity to reproduction reveal no special hazard for humans.

No organ-specific toxicity of rivaroxaban was observed up to the highest doses tested.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

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

Film-coating
Hypromellose (E464)
Titanium dioxide (E171)
Macrogol 400 (E1521)
Yellow iron oxide (E172)
Water, purified

6.2 Incompatibilities

None Known

6.3 Special precautions for storage

Do not store above 30°C.

6.4 Nature and contents of container

Aluminium-PVC/PE/PVdC blisters of 56 tablets.

6.5 Instructions for use / handling

None

7. MANUFACTURER

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8. DATE OF REVISION OF TEXT

Jun 2023