120 mm
(Front)

480 mm

Xarelto®
(Rivaroxaban)

Tablets

BOX WARNINGS

(A) PREMATURE DISCONTINUATION OF RIVAROXABAN INCREASES THE RISK OF THROMBOTIC EVENTS, (B) SPINAL/EPIDURAL HEMATOMA

A. Premature Discontinuation of Rivaroxaban Increases the Risk of Thrombotic Events
Premature discontinuation of any oral anticoagulant, including rivaroxaban, increases the risk of thrombotic events. If anticoagulation with Rivaroxaban is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant

B. Spinal/epidural Hematoma
Epidural or spinal hematomas have occurred in patients treated with Rivaroxaban who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas may result in long-term or permanent paralysis. Consider these risks when scheduling patients for spinal procedures.

DOSAGE FORM
Each film-coated tablet contains
Rivaroxaban 10mg

INDICATIONS
Rivaroxaban is indicated for the prevention of venous thromboembolism (VTE) in Patients undergoing major orthopaedic surgery of the lower limbs.

DOSAGE AND METHOD OF ADMINISTRATION
VTE prevention - Dosage and method of administration VTE prevention
VTE prevention - Method of administration
Oral use
VTE prevention, Recommended usual dose
The recommended dose for VTE prevention in major orthopaedic surgery is one 10 mg tablet once daily.
VTE prevention: Duration of treatment
After major hip surgery patients should be treated for 5 weeks
After major knee surgery patients should be treated for 2 weeks.
VTE prevention, Method and frequency of administration
One 10 mg tablet of Rivaroxaban should be taken once daily.
Rivaroxaban 10 mg tablets may be taken with or without food.
The initial dose should be taken within 6-10 hours after surgery provided that hemostasis has been established.
VTE prevention: Missed Dose
If a dose is missed the patient should take the 10 mg rivaroxaban dose immediately and continue on the following day with the same daily intake as before.
VTE prevention - Dosage and method of administration
Additional information on special populations
Patients with Hepatic impairment
Rivaroxaban is contraindicated in patients with hepatic disease which is associated with coagulopathy leading to a clinically relevant bleeding risk (see section 'Contraindications').
Patients with renal impairment
No dose adjustment is required if rivaroxaban is administered to patients with mild or moderate renal impairment.
Limited clinical data for patients with severe renal impairment indicate that rivaroxaban plasma levels are significantly increased in this patient population. Therefore rivaroxaban must be used with caution in these patients (see section 'Special warnings and precautions for use'). Use of rivaroxaban not recommended in patients with CrCl <15 ml/min (see section 'Special warnings and precautions for use').
Converting from Vitamin K Antagonists (VKA) to Rivaroxaban
When converting patients from VKA to rivaroxaban, INR values will be falsely elevated after the intake of rivaroxaban. The INR is not valid to measure the anticoagulant activity of rivaroxaban and therefore should not be used (see section 'Interactions with other medicinal products and other forms of interaction').
Converting from rivaroxaban to Vitamin K antagonists (VKA)
There is a potential for inadequate anticoagulation during the transition from rivaroxaban to VKA. Continuous adequate anticoagulation should be ensured during any treatment to an alternate anticoagulant. It should be noted that rivaroxaban can contribute to an elevated INR.
In patients converting from rivaroxaban to VKA, VKA should be given concurrently until the INR is >2.0. For the first two days of the conversion period, standard VKA dosing should be used followed by VKA dosing guided by INR testing. Most patients can switch from rivaroxaban and VKA, the INR should not be tested earlier than 24 hours after the previous dose for the next dose of rivaroxaban. Once rivaroxaban is discontinued INR testing may be done to ensure 24 hours after the last dose (see section 'Interaction with other medicinal products and other forms of interaction').
Converting from parenteral anticoagulants to Rivaroxaban
For patients currently receiving a parenteral anticoagulant, start rivaroxaban 0 to 2 hours before the time of the next scheduled administration of the parenteral drug (e.g. LMWH) or at the time of discontinuation of a continuously administered parenteral drug (e.g. intravenous unfractionated heparin).
Converting from rivaroxaban to parenteral anticoagulants
Discontinue rivaroxaban and give the first dose of parenteral anticoagulant at the time that the next rivaroxaban dose would be taken.
Children and adolescents
(From birth to 18 or 18 years depending on local law)
Safety and efficacy data not been established in children and adolescents (aged 18 years).
Geriatric patients
No dose adjustment is required based on age
Gender
No dose adjustment is required based on gender
Body weight
No dose adjustment is required based on body weight
Ethnic differences
No dose adjustment is required based on ethnic differences.

CONTRAINDICATIONS
Rivaroxaban is contraindicated in patients with hypersensitivity to rivaroxaban or any excipient of the tablet.
Rivaroxaban is contraindicated in patients with clinically significant active bleeding (e.g. Gastrointestinal bleeding, gastrointestinal bleeding).
Rivaroxaban is contraindicated in patients with organ disease which is associated with coagulopathy leading to clinically relevant bleeding risk.
Safety and efficacy of Rivaroxaban have not been established in pregnant women. Animal data show that rivaroxaban crosses the placental barrier. Therefore use of Rivaroxaban is contraindicated throughout pregnancy (see section 'Pregnancy and lactation').
Safety and efficacy of Rivaroxaban has not been established in lactating women. Animal data indicate that rivaroxaban is secreted into breast milk. Therefore Rivaroxaban may only be administered after breast feeding is discontinued (see section 'Pregnancy and lactation').

A. SPECIAL WARNINGS AND PRECAUTIONS FOR USE
Premature Discontinuation of Rivaroxaban Increases The Risk Of Thrombotic Events
Premature discontinuation of any oral anticoagulant, including rivaroxaban, increases the risk of thrombotic events. If anticoagulation with Rivaroxaban is discontinued for a reason other than pathological bleeding or completion of a course of therapy, consider coverage with another anticoagulant.
B. Spinal/epidural Hematoma
Epidural or spinal hematomas have occurred in patients treated with Rivaroxaban who are receiving neuraxial anesthesia or undergoing spinal puncture. These hematomas 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 hematomas in these patients include:
- use of indwelling epidural catheters
- concomitant use of other drugs that affect hemostasis, such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors, other anticoagulants
- a history of traumatic or repeated epidural or spinal puncture
- a history of spinal deformity or spinal surgery
- optimal timing between the administration of Rivaroxaban and neuraxial procedures is not known
- Monitor patients frequently for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary. Consider the benefits and risks before neuraxial intervention in patients anticoagulated or to be anticoagulated for thrombosis prophylaxis.

CONCOMITANT MEDICATION
Rivaroxaban 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 concentration to a clinically relevant degree (2.6-fold on average) which may lead to an increased bleeding risk (see section 'Interaction with other medicinal products and other forms of interaction'). The Azole-antimycotic fluconazole, a moderate CYP 3A4 inhibitor, has minor less effect on rivaroxaban exposure and can be co-administered (see section 'Interaction with other medicinal products and other forms of interaction').
Renal impairment
Rivaroxaban is to be used with caution in patients with moderate renal impairment receiving concomitantly leading to increased rivaroxaban plasma concentrations (see section 'Interaction with other medicinal products and other forms of interaction'). In patients with severe renal impairment, rivaroxaban (Xarelto tablets) may be significantly elevated (1.9-fold on average) which may lead to an increased bleeding risk.
Due to limited data rivaroxaban should be used with caution in patients with CrCl <30 ml/min.
No clinical data are available for patients with severe renal impairment (CrCl <15 ml/min). Therefore use of rivaroxaban is not recommended in these patients (see section 'Dosage and method of administration').
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 (see section 'Interaction with other medicinal products and other forms of interaction').
This may be done by regular physical examination of the patient, close observation of the surgical wound drainage and periodic measurements of hemoglobin.
VTE prevention: Hip fracture surgery
Rivaroxaban has not been studied in international clinical trials in patients undergoing hip fracture surgery. Limited clinical data from a non-interventional study are available for patients undergoing hip fracture surgery (see Xarelto tablet in hip fracture surgery).
Bleeding risk
Rivaroxaban like other antithrombotics should be used with caution in patients with an
Increased bleeding risk such as
- Congenital or acquired bleeding disorders
- uncontrolled severe arterial hypertension
- Active ulcerative gastrointestinal disease
- Recent gastrointestinal ulcerations
- Vascular retinopathy
- Recent intracranial or intraspinal hemorrhage
- Intraspinal or intracerebral vascular abnormalities
- Recent brain, spinal or ophthalmological surgery
- Bronchiectasis or history of pulmonary bleeding

Care should be taken if patients are treated concomitantly with drugs affecting hemostasis such as non-steroidal anti-inflammatory drugs (NSAIDs), platelet aggregation inhibitors or other antithrombotics.
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.
VTE prevention: 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 noticed, urgent diagnosis and treatment is necessary.
The physician should consider the potential benefits versus the risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis. An epidural catheter should not be withdrawn earlier than 18 hours after the last administration of rivaroxaban.
Rivaroxaban should be administered at earliest 6 hours after the removal of the catheter.
If traumatic puncture occurs the administration of rivaroxaban is to be delayed for 24 hours.
Surgery and interventions
If an invasive procedure or surgical intervention is required, rivaroxaban 10 mg should be stopped at least 24 hours before the intervention, if possible and based on clinical judgment of the physician.
If the procedure cannot be delayed, the increased risk of bleeding should be assessed against the urgency of the intervention.
Rivaroxaban should be restarted as soon as possible after the invasive procedure or surgical intervention provided the clinical relevance allows and adequate hemostasis has been established.
Women of childbearing potential
Rivaroxaban should be used in women of childbearing potential only with effective contraception.
Interaction with other medicinal products and other forms of interaction
Pharmacodynamic interactions
Rivaroxaban is cleared mainly via cytochrome P450-mediated (CYP 3A4, CYP 2J) hepatic metabolism and renal excretion of the unchanged drug, involving the P-glycoprotein (P-gp) breast cancer resistance protein (BCRP) transporter System.
CYP Inhibition
Rivaroxaban does not inhibit CYP 3A4 or any other major CYP isoforms.
CYP Induction
Rivaroxaban does not induce CYP 3A4 or any other major CYP isoforms.
Effects on rivaroxaban
The concomitant use of rivaroxaban with strong CYP 3A4 and P-gp inhibitors, may lead to to increased hepatic and renal drug uptake and thus significantly increased systemic exposure.
Co-administration of rivaroxaban 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 maximum plasma drug (AUC and a 1.7-fold increase in mean maximum Cmax, with significant increase in the pharmacodynamic effects.
Co-administration of rivaroxaban with the HIV protease inhibitor Ritonavir (600 mg twice daily), a strong CYP 3A4 and P-gp inhibitor, led to a 2.2-fold increase in mean maximum AUC and a 1.6-fold increase in mean maximum Cmax, with significant increase in the pharmacodynamic effects.
Therefore, rivaroxaban is not recommended in patients receiving concomitant systemic treatment with azole-antimycotics or HIV protease inhibitors (see section 'Special warnings and precautions for use').
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 maximum AUC and a 1.4-fold increase in Cmax. This increase which is close to the magnitude of the normal variability of AUC and Cmax, 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 maximum AUC and Cmax. The increase is within the magnitude of the normal variability of AUC and Cmax, and is considered as clinically not relevant.
Fluconazole (400 mg once daily), considered as moderate CYP 3A4 inhibitor, led to a 1.9-fold increase in mean maximum AUC and a 1.3-fold increase in mean Cmax. This increase is within the magnitude of the normal variability of AUC and Cmax, and is considered as clinically not relevant (see section 'Special warnings and precautions for use').
Co-administration of rivaroxaban with the strong CYP 3A4 and P-gp inducer rifampicin led to an approximate 50% decrease in mean maximum AUC, with parallel decrease in its pharmacodynamic effects.
The concomitant use of rivaroxaban with other strong CYP 3A4 inducers (e.g. phenytoin, carbamazepine, phenobarbitone or St. John's Wort) may also lead to a decrease in rivaroxaban plasma concentrations.
The decrease in rivaroxaban plasma concentrations is considered as clinically not relevant for patients treated with 10 mg rivaroxaban since they for prevention of VTE after major orthopedic surgery of the lower limbs.
Pharmacodynamic Interactions
After co-ingestion of rivaroxaban (10 mg single dose) with (10 mg single dose) no additive effect on activated Xa activity was observed without any additive effects on clotting tests (PT, aPTT). Enoxaparin did not affect the pharmacokinetics of rivaroxaban (see section 'Special warnings and precautions for use').
Co-ingestion (30 mg loading dose followed by 75 mg maintenance dose) did not show a pharmacodynamic interaction with rivaroxaban (15 mg) for a relevant number of bleeding times was observed in a subset of patients which correlated to platelet aggregation, P-selectin or GPIIb / IIIa complex levels (see note in 'Special warnings and precautions for use').
No clinically relevant prolongation of bleeding time was observed after Co-ingestion rivaroxaban (10 mg and 500 mg aspirin). Nonetheless there may be individuals with more pronounced pharmacodynamic response (see section 'Special warnings and precautions for use').
Concomitant intake with ASA (325 mg) or Clopidogrel (75mg) or from rivaroxaban
(30 mg) to rivaroxaban (20 mg) increased prothrombin time/INR (Neoplastin), bore than additively individual INR values up to 12 (higher Xarelto), 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, PCT, and Heptest can be used as these tests were not affected by enoxaparin. From day 4 after stopping enoxaparin, results 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 rivaroxaban during the conversion period, INR measurements can be used. At the Through of rivaroxaban (24 hours after the previous intake of rivaroxaban) as the test is minimally affected by rivaroxaban at this time point.
No pharmacokinetic interaction was observed between warfarin and Rivaroxaban.
Food and Dairy Products
10 mg rivaroxaban can be taken with or without food.
Interactions with laboratory parameters
Clotting parameters (PT, aPTT, HepTest) are affected as expected by the mode of action of rivaroxaban.

PREGNANCY AND LACTATION
Women of childbearing potential/Contraception
Rivaroxaban should be used in women of childbearing potential only with effective contraception.
Pregnancy
Safety and efficacy of rivaroxaban have not been established in pregnant women.
In rats and rabbits, rivaroxaban showed pronounced maternal toxicity with placental change related to the pharmacological mode of action (e.g. hemorrhage, complications leading to reproductive toxicity. No primary teratogenic potential was identified. Due to the intrinsic risk of bleeding and the evidence that rivaroxaban passes the placenta, rivaroxaban is contraindicated in pregnancy (see section 'Contraindications').
Safety and efficacy of rivaroxaban have not been established in nursing mothers. In rats rivaroxaban is excreted into the breast milk. Therefore rivaroxaban may be administered after breastfeeding is discontinued (see section 'Contraindications').
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 section 'Undesirable effects'). Patients in presenting these adverse reactions should not drive or use machines.

ADVERSE REACTIONS
The frequencies of ADRs Reported with Rivaroxaban are summarized in the table below. Frequencies are defined as: very Common (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1000 to < 1/100); Rare (≥ 1/10,000 to < 1/1000); Very rare (< 1/10,000).

* By spontaneous adverse reactions, contact Sanofi Company Limited Medical Affairs Department or email at medical.affairs@sanofi.company.com

System Organ Class (MedDRA)	Common	Uncommon	Rare
Blood and the lymphatic system disorders	Anemia (incl. respective laboratory parameters)	Thrombocythemia (incl platelet count increased)	
Cardiac Disorders		Tachycardia	
Eye disorder	Eye Hemorrhage (incl conjunctival hemorrhage)		
Gastrointestinal Disorders	Gingival bleeding Gastrointestinal hemorrhage (incl rectal hemorrhage) Gastro-intestinal and abdominal pains Dyspepsia Nausea Constipation* Diarrhea Vomiting*	Dry mouth	
General Disorders and administration site conditions	Fever* Edema peripheral Decreased general strength and energy (incl. fatigue and asthenia)	Feeling unwell (incl. malaise)	Localized edema*
Hepato-biliary disorder		Hepatic function abnormal	jaundice
Immune system disorders		Allergic reaction Dermatitis allergic	
Injury, poisoning and post procedural complications	Post procedural hemorrhage (incl. postoperative anemia and wound hemorrhage) contusion	Wound Secretion *	Vascular pseudo aneurysm
Investigations	Increase transaminases	Increase Bilirubin Increase in blood alkaline Phosphatase * Increase in LDH Increase in Lipase * Increase in amylase * Increase in GGT	Bilirubin Conjugated increased (with or without concomitant increase of ALT)
Musculoskeletal, connective tissue and bone disorders	Pain in extremity *	Hemarthrosis	Muscle hemorrhage
Nervous system Disorders	Dizziness Headache	Cerebral and intracranial hemorrhage Syncope	
Renal and urinary disorders	Urogenital incl. Hemorrhage (incl. hematuria and menorrhagia *) Renal impairment incl. Blood creatine increased, Blood urea increased*		
Respiratory tract disorders	Epistaxis Hemoptysis		
Skin and subcutaneous tissue disorders	Pruritus (incl. uncommon cases of generalized pruritus) Rash Ecchymosis Cutaneous and subcutaneous hemorrhage		
Vascular disorders	Hypotension Hematoma		

* Observed after major orthopedic surgery of the lower limbs
* Data not in VTE treatment as only common frequency (≥ 1/100)
<ADR commission is based on MedDRA.
Post Marketing Experience
The following adverse reactions have been identified during post-approval use of rivaroxaban.
Immune System Disorders: angioedema and allergic oedema
Hepato-biliary Disorder: Cholestasis, Hepatitis (incl hepatocellular injury)
Blood and lymphatic system disorder: Thrombocytopenia

OVERDOSE
Rare cases of overdose have been reported without bleeding complications or other adverse reactions. Due to limited absorption it is associated with no further increase in average plasma exposure to injection of supratherapeutic doses of 50 mg or above.
A specific antidote antagonizing the pharmacodynamic effects of rivaroxaban is not available. The use of activated charcoal to reduce absorption of risk of rivaroxaban overdose may be considered. Due to the high plasma protein binding rivaroxaban is not expected to be dialysable.
Management of Bleeding
Due to a bleeding complication, stop to a patient receiving rivaroxaban, the next administration should be delayed or treatment should be discontinued as appropriate.
Rivaroxaban has a half-life approximately 5 to 11 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, antidote of a specific coagulant reversal agent should be considered, such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC), or recombinant factor VIII (rFVIIa). Have, at, there is currently very limited clinical experience with the use of these product - individuals receiving rivaroxaban. 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 aminomaxilic acid and aprotinin in individuals receiving rivaroxaban. There is neither scientific rationale for benefit nor experience with systemic hemostatic agents (aprotinin) in individuals receiving rivaroxaban.

PRESENTATION
Xarelto (Rivaroxaban) 10 mg tablets are available in strip blister pack of 10 Tablets

INSTRUCTIONS
- To be used on prescription of a registered medical practitioner only
- Protect from moisture, freezing, excessive heat and sunlight.
- Keep out of the reach of children
- Do not crush (refer to leaflet for more information).

Mfg. Sanofi Spain
SEARLE
Manufactured by
The Searle Company Limited
F-319, S.I.T.E., Karachi Pakistan

15B5311107

120 mm
(Back)