Review Article

A Review on Rivaroxaban: A Prominent Oral Anti-coagulant Agent

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ABSTRACT

Rivaroxaban (Xarelto®) is an oral oxazolidinone-based anticoagulant agent. It inhibits not only free factor Xa with high selectivity but also prothrombinase bound and clot-associated factor Xa in a concentration-dependent manner. It is a potent, selective direct inhibitor of factor Xa that is used in the prevention of venous thromboembolism (VTE) in adult patients after total hip replacement (THR) or total knee replacement (TKR) surgery. The recommended dose of Xarelto is 10 mg taken orally once daily. For a 10 mg dose, the oral bioavailability of Rivaroxaban is high (80–100%) and is not affected by food intake. These pharmacological properties underpin the use of Rivaroxaban in fixed dosing regimens, with no need for dose adjustment or routine coagulation monitoring. The drug is metabolized to inactive metabolites in liver, half of which is excreted by kidneys and other half is excreted via faecal route. CYP3A4, CYP345, and CYP2J2 catalyze the hepatic metabolism of Rivaroxaban. This paper reviews the pharmacological and pharmaceutical properties of Rivaroxaban (Xarelto).

Keywords: Rivaroxaban, Coagulation, Thrombin, Prothrombin, Pharmacokinetics.

INTRODUCTION

Anticoagulant agents are the upholder for the prevention and treatment of arterial and venous thrombosis. For the treatment and prevention of thrombosis, several anticoagulants are available, such as vitamin K antagonists and low-molecular-weight heparins (LMWHs) but they are not targeted, means that they inhibit more than one enzyme in the coagulation cascade. Clinically anticoagulant therapy is used in the prevention of venous thromboembolism (VTE) after surgery to prophylactic stroke prevention in patients with atrial fibrillation. In recent years, new anticoagulants targeting single component of the coagulation cascade have been developed[1,2].

Coagulation factor X is a vitamin-K-dependent plasma protein. It play potent role in the regulation of blood coagulation by converting prothrombin into thrombin. The central position in the coagulation cascade is occupies by activated Factor X (FXa). FXa forms a linkage in the intrinsic and extrinsic coagulation pathways, and acts as the rate-limiting step in thrombin production. By blocking FXa it inhibits the thrombin generation[3,4].

Rivaroxaban, is the first bioavailable orally administered direct factor Xa inhibitor. It selectively and reversibly blocks the active site of factor Xa and does not require a cofactor (such as Anti-thrombin III) for activity[5]. Rivaroxaban was invented and manufactured by Bayer and is marketed as Xarelto[6,7]. It is the first available orally active direct factor Xa inhibitor. It is used for the prevention of venous thromboembolism (VTE) in patients undergoing elective hip or knee replacement surgery, for the treatment of VTE, prevention of stroke in those with atrial fibrillation, and prevention of cardiovascular events in patients with acute coronary syndrome[8-10].

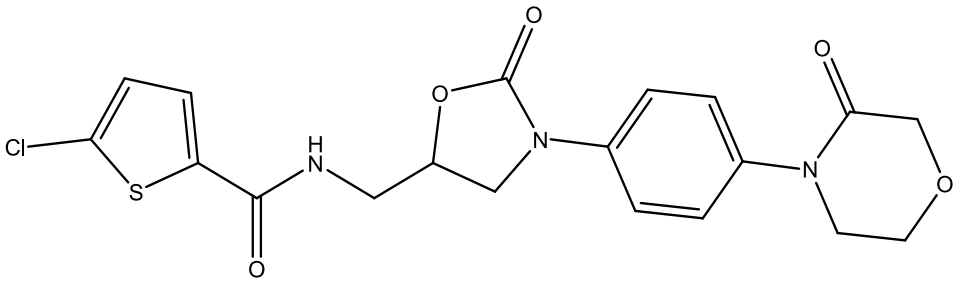
CHEMISTRY

Trade Name: Xarelto

Formula: $C_{19}H_{18}ClN_3O_5S$

Molecular Mass: 435.882

Rivaroxaban is an oxazolidinone derivative. It is odorless, non-hygroscopic, white to yellowish powder, with chirality (S)-enantiomer. Rivaroxaban is practically insoluble in water. Rivaroxaban p^{Ka1} value is13.4 [11,12]



5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide

MECHANISM OF ACTION

Rivaroxaban is an oral direct, reversible, competitive, rapid and dose-dependent, inhibitor of FXa (Figure 1). FXa catalyzes the reaction that converts factor II (prothrombin) to factor IIa (thrombin)[13-16]. Inhibition of FXa activity by rivaroxaban inhibits thrombin generation via both pathways as the FXa acts at the convergence of the contact activation (intrinsic) and tissue factor (extrinsic) pathways[16-19].

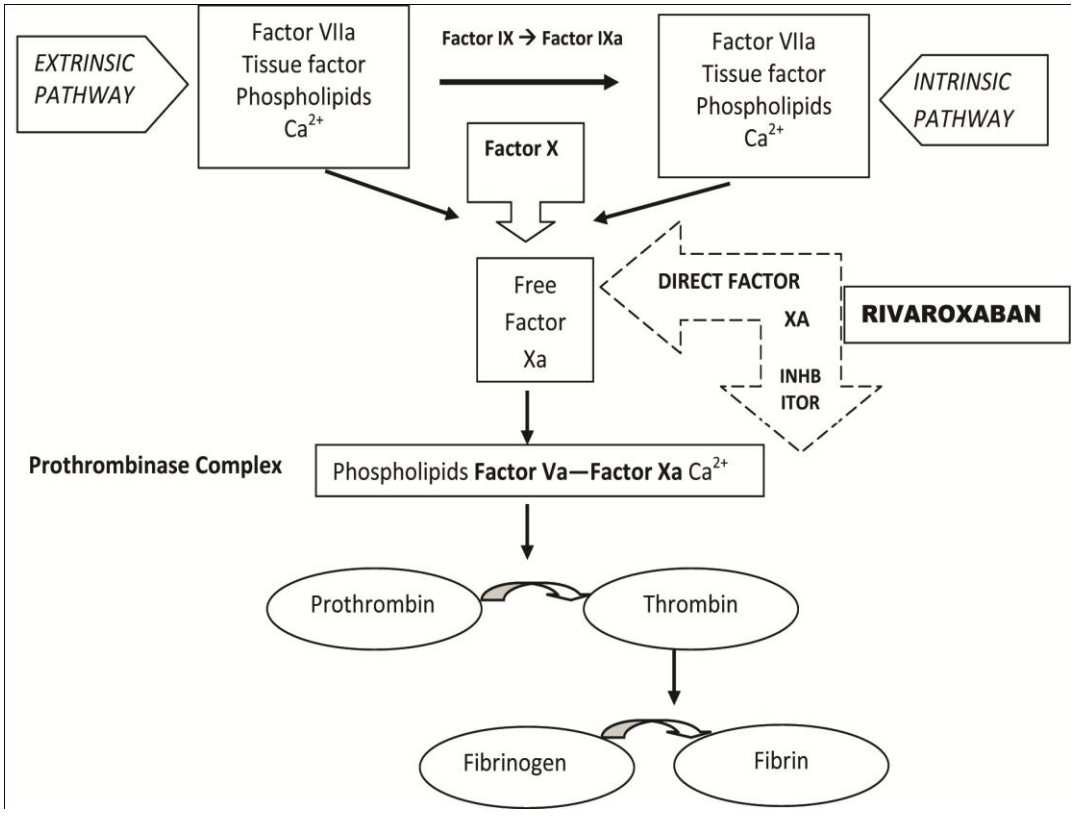


Fig. 1: Schematic representation of the coagulation cascade

FXa catalyzes prothrombin activation via the prothrombinase complex, which consists of FXa, factor II, factor Va, calcium ions, and phospholipid as embled on the surface of activated platelets[20,21]. It is a potent oral direct inhibitor of the serine endopeptidase factor Xa and inhibits both free factor Xa and factor Xa bound in the prothrombinase complex. Rivaroxaban inhibits FXa with more than 100,000-fold greater selectivity than other biologically relevant serine proteases[22-26].

DOSAGE

The recommended dose of Xarelto is 10 mg taken orally once daily. The initial dose should be taken at least 6 to 10 hours after surgery once hemostasis has been established. It is recommended 35 day treatment-- For patients undergoing hip replacement surgery and 14 day treatment- For patients undergoing knee replacement surgery The use of doses of more than 10 mg of once daily or treatment beyond 35 days is not recommended[27].

PHARMACOLOGY

❖ **Pharmacodynamics**

Dose-dependent inhibition of FXa activity was observed in humans anti-factor Xa activity is also influenced by Rivaroxaban. The dose-proportional pharmacodynamic effect of Rivaroxaban as an anticoagulant agent was demonstrated[19,22,28].

Maximum FXa activity inhibitory effect (Emax) for multiple doses of 5 mg twice daily to 30 mg twice daily: 20–70% depending on dose. The time E_{max} is 1-4 hr. The half life of the FXa activity inhibition of Rivaroxaban is about 6-7 hour[29].The maximum prothrombin time (PT) prolongattion for multiple doses of 5-30 mg twice daily is about 1.3-2.6 times baseline depemding on dose. The time to maximum PT prolongation is 1-4 hour[30]. Rivaroxaban maximum activated partial thromboplastin time prolongation for multiple doses of 5-30 mg twice daily is about 1.3-1.8 times baseline depemding on dose. Time to maximum activated partial thromboplastin time prolongation is 1-4 hour[31- 33].

❖ **Pharmacokinetics**

Absorption

Rivaroxaban pharmacokinetics following oral administration is best described by a one-compartment model. Rivaroxaban absolute bioavailability is dose-dependent. For the 10 mg dose, it is estimated to be 80% to 100% and is not affected by food. Coadministration of Xarelto with food increases the bioavailability of the 20 mg dose (mean AUC and Cmax increasing by 39% and 76% respectively with food). The maximum concentrations (Cmax) of rivaroxaban appear 2 to 4 hours after tablet intake. The pharmacokinetics of Rivaroxaban is not affected by drugs altering gastric pH[19,34-36].

Coadministration of Rivaroxaban with the H_2-receptor antagonist and antacid did not show an effect on the bioavailability and exposure of Rivaroxaban. Absorption of Rivaroxaban is dependent on the site of drug release in the GI tract. The decrease in release in proximal small intestine of 29% and 56% in AUC and Cmax respectively of tablet was compared to granulate. 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[22,37-39].

Distribution

The main binding site is albumin for the plasma protein. The binding of Rivaroxaban in human plasma is approximately 92% to 95%, with albumin. The steady-state volume of distribution in healthy subjects is approximately 50 L[25, 40].

Metabolism

Two thirds of the drug is metabolized to inactive metabolites in liver, half of which is excreted by kidneys and other half is excreted via faecal route. CYP3A4, CYP345, and CYP2J2 catalyze the hepatic metabolism of Rivaroxaban[32,41, 42].

Excretion

After oral administration, approximately one-third of the absorbed dose is excreted unchanged in the urine, with the remaining two-thirds excreted as inactive metabolites in both the urine and faeces. Oral administration of a [^{14}C] - Rivaroxaban dose, 66% of the radioactive dose was recovered in urine (36% as unchanged drug) and 28% was recovered in faces (7% as unchanged drug). In urine the unchanged drug is excreted out[43].

As a significant portion of Rivaroxaban is excreted via kidneys, renal impairment is expected to increase the concentration of the drug, with increasing severity of renal impairment causing more retention of the drug[44,45].

THERAPUTIC EFFICAY[45-53]

1. **Decreases the Risk of Stroke and Systemic Embolism in Nonvalvular Atrial Fibrillation:** In the patients with nonvalvular atrial fibrillation Rivaroxaban is indicated to reduce the risk of stroke and systemic embolism.
2. **Treatment of Deep Vein Thrombosis:** The dru**g** is indicated for the treatment of deep vein thrombosis (DVT).
3. **Treatment of Pulmonary Embolism:** Rivaroxaban indicated for the treatment of pulmonary embolism (PE).
4. **In Reductionof the Risk of Recurrence of Deep Vein Thrombosis and of Pulmonary Embolism:** Xarelto indicated for the reduction in the risk of recurrence of deep vein thrombosis and of pulmonary embolism following initial 6 months treatment for DVT and PE.
5. **Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery:** The drug is indicated for the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery.

ADVERSE EVENTS

Like any other anticoagulant, oral FXa inhibitor major adverse event is bleeding. So far, bleeding has been comparable to other active comparators and seems to be dependent on the dose. Other common adverse effects, includes headache, nausea and Spinal/epidural hematoma[54].

Bleeding is the most serious adverse event with any anticoagulant. There is currently no antidote for rivaroxaban (unlike warfarin, the action of which can be reversed with vitamin K or prothrombin complex concentrate). The internal bleeding due to adverse event is difficult to manage 'Andexanet alfa' is possible antidote which is being investigated[55-57].

WARNING AND PRECAUTIONS[34,46,58,59]

1. **It may increase the risk of thrombotic events after premature discontinuation** Premature discontinuation of any Rivaroxaban increases the risk of thrombotic events. An increased rate of stroke was observed during the transition from Xarelto to warfarin in clinical trials in atrial fibrillation patients.
2. **Risk of bleeding:** The drug increases the risk of bleeding and can cause serious or fatal bleeding. Discontinue Xarelto in patients with active pathological haemorrhage. Concomitant use of other drugs that impair haemostasis increases the risk of bleeding, eg: aspirin, P2Y12 platelet inhibitors, other antithrombotic agents, fibrinolytic therapy, and non-steroidal anti-inflammatory drugs (NSAIDs).
3. **Spinal/Epidural anesthesia or puncture:** The patients treated with anticoagulant agents for prevention of thromboembolic complications in neuraxial anesthesia (spinal/epidural anesthesia) or spinal puncture is employed, are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.
4. **Use in patients with renal impairment:** Discontinue Xarelto in patients who develop acute renal failure. The patients with CrCl <15 mL/min should avoid the use of drug as the drug exposure is increased.
5. **Use with P-gp and strong Cyp3a4 inhibitors or inducers:** Avoid concomitant use of Xarelto with combined P-gp and strong CYP3A4 inhibitors e.g: ketoconazole, itraconazole, ritonavir.
6. **Risk of pregnancy-related haemorrhage:** In pregnant women, Xarelto should be used only if the potential benefit justifies the potential risk to the mother and foetus. Its use may cause blood loss eg: loss of haemoglobin.
7. **Patients who require thrombolysis or pulmonary embolectomy:** Xarelto is not recommended as an alternative to unfractionated heparin in patients with pulmonary embolism, who had receive thrombolysis or pulmonary embolectomy.

PHARMACOECONOMICS

In several modelled cost-effectiveness analyses concluded that, Rivaroxaban was predicted to be cost effective. Cost effectiveness was demonstrated irrespective of surgical procedure duration of treatment or dosage regimen[60].

DRUG INTERACTION

- **Drugs that inhibit Cytochrome P450 3A4 enzymes and drug transport systems**

The concomitant use of Rivaroxaban with P-gp and CYP3A4 inhibitors eg: ketoconazole, ritonavir, clarithromycin, erythromycin and fluconazole, increases in rivaroxaban exposure and pharmacodynamic effects[17-20,61].

- **Drugs that induce Cytochrome P450 3A4 enzymes and drug transport systems**

Studies indicate that coadministration of the drug with a combined P-gp and strong CYP3A4 inducer (e.g., rifampicin, phenytoin) decreased Rivaroxaban exposure by up to 50%. Similar decreases in pharmacodynamic effects were also observed. These decreases in exposure to Rivaroxaban may also decrease efficacy[30,62].

- **Anticoagulants and NSAIDs/Aspirin**

Bleeding risk may be increased when NSAIDs are used concomitantly with Xarelto Concomitant aspirin use has been identified as an independent risk factor for major bleeding in efficacy trials. NSAIDs are known to increase bleeding. Avoid concurrent use of Xarleto with other anticoagulants due to increased bleeding risk unless benefit outweighs risk[32,63-65].

- **Drug-Disease Interactions with Drugs that Inhibit Cytochrome P450 3A4 Enzymes and Drug Transport Systems**

Patients with renal impairment coadministered Xarelto with drugs classified as combined P-gp and moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, dronedarone, and erythromycin) have increased exposure compared with patients with normal renal function and no inhibitor use. Significant increases in Rivaroxaban exposure may increase bleeding risk[15,33,66-68].

USE IN SPECIAL POPULATION

Various studies have also been undertaken to define the pharmacokinetic and pharmacodynamic profile and safety of Rivaroxaban in various subpopulations of patients.

1. Effects of body weight and gender

The pharmacokinetics and pharmacodynamics of Rivaroxaban 10 mg in a single-blind, placebo-controlled study in healthy male and female subjects were unchanged over the weight range 45–173 kg. This suggest that the drug can be used at a fixed dose irrespective of weight . Nature of adverse events in the healthy volunteers studied shows no differences owing to body weight in the incidence. Gender did not affect the pharmacokinetic or pharmacodynamic profile of Rivaroxaban 10 mg[34,69-71].

2. Effects of age and renal impairment

With a prolongation of the half-life up to 13 hr, overall exposure to Rivaroxaban AUC was higher in elderly than in younger individuals. Consistent with this, studies in otherwise healthy volunteers have demonstrated that renal impairment results in decreased renal clearance of a single Rivaroxaban 10 mg dose and increases overall exposure to the drug . A recent study confirmed increased plasma exposure and pharmacodynamic effects in subjects with increasing renal impairment. However, the influence of renal function on rivaroxaban clearance was moderate, as expected for a drug only partially renally excreted[72].

3. Effects of hepatic impairment

There were no relevant differences in the pharmacokinetic or pharmacodynamic profile of Rivaroxaban inpatients with mild hepatic impairment after a single 10 mg dose. Consequently, Rivaroxaban is contraindicated in patients with significant hepatic disease associated with coagulopathy leading to a clinically relevant bleeding risk[73,74].

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