

RIVAROXABAN

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INTRODUCTION:

Rivaroxaban (XARELTO) is an orally bioavailable direct Factor Xa (FXa) inhibitor that selectively blocks the active site of FXa and does not require a cofactor (such as antithrombin III) for activity. Activation of Factor X to FXa, via the intrinsic and extrinsic pathways, plays a central role in the cascade of blood coagulation.

XARELTO is approved by the FDA for multiple indications:

- Reducing stroke risk and systemic embolism in patients (pts) with nonvalvular atrial fibrillation (AF)⁵.
- Treatment of acute DVT, PE, and risk reduction of DVT/PE recurrence, following initial 6 months of anticoagulation^{3,4}.
- DVT prophylaxis which may lead to PE in pts undergoing knee or hip replacement surgery⁶.

Pharmacologic Profile:

>*Rapid onset of action:* Xarelto reaches maximum plasma concentration, inhibiting FXa at 2-4 hrs after intake.

>*Clearance is dual:* approximately 1/3 excreted unchanged renally and approximately 2/3 metabolized in the liver. Elimination half-life is 5 to 9 hours in healthy subjects aged 20 to 45 and 11 to 13 hours in the elderly.

>*Bioavailability:* A 10 mg dose of Xarelto has nearly complete bioavailability and is not affected by food. A 15 and 20 mg dose has nearly complete bioavailability when taken with food.

>*Body Weight Extremes:* (<50 kg or >120 kg) did not influence rivaroxaban exposure. No clinical data are available for pts. with severe hepatic impairment. Rivaroxaban should be avoided in pts. with moderate (Child-Pugh B) or severe (Child-Pugh C) hepatic impairment or any hepatic disease associated with coagulopathy.

Dosing:

Stroke reduction in pts. with nonvalvular atrial fibrillation:

- One 20-mg tablet with the evening meal in patients with CrCl >50 mL/min or
- One 15-mg tablet with the evening meal recommended for patients with CrCl 15-50 mL/min.

Treatment of DVT and PE:

- 15 mg twice daily with food for first 21 days. On day 22 change to 20 mg once daily with food for remaining treatment.

Note: no dose reduction needed in patients with mild renal insufficiency, but **not recommended** for use in pts. with CrCl <30 mL/min.

Prophylaxis of DVT after knee and hip replacement surgery:

- 10 mg daily at least 6-10 hours after surgery. Duration is 12 days after knee and 35 days after hip replacement surgery.

Advantages of Rivaroxaban:

- Eliminates need for bridging with parenteral heparin or LMWH heparin to oral therapy
- Rapid onset of anticoagulation
- No routine monitoring of INR or any other coagulation parameters required
- Low potential for drug interactions
- No dose adjustments for age, weight, or gender
- No known dietary restrictions
- Oral dosing throughout treatment

Conversion to Rivaroxaban.

- Switching pts. from warfarin: Discontinue warfarin and start rivaroxaban when INR is below 3.0.
- Switching pts. from anticoagulants other than warfarin: Start rivaroxaban 0 to 2 hrs prior to the next scheduled evening dose of the other anticoagulant and omit administration of the other anticoagulant. For unfractionated heparin being administered by continuous infusion, stop infusion and begin rivaroxaban at the same time.
- For pts. currently taking rivaroxaban and transitioning to an anticoagulant with rapid onset, discontinue rivaroxaban and give first dose of other anticoagulant (oral or parenteral) at the time the next rivaroxaban dose would have been taken.

Switching from Rivaroxaban to warfarin

- No clinical trial data available to guide converting pts. from rivaroxaban to warfarin.
- Rivaroxaban affects INR, so INR measurements made during coadministration with warfarin may not be useful for determining appropriate dose of warfarin. One approach is to discontinue rivaroxaban and

begin both parenteral anticoagulant and warfarin at the time the next dose of rivaroxaban would have been taken.

Perioperative Management:

If anticoagulation must be discontinued to reduce risk of surgical bleeding, rivaroxaban should be stopped 1-2 days prior to surgeries or invasive procedures in pts. with normal renal function; or earlier in pts. with impaired renal function undergoing surgery with high risk of bleeding. Rivaroxaban should be restarted when adequate hemostasis has been established.

An epidural catheter should not be removed earlier than 18 hrs after the last administration of rivaroxaban. The next dose is not to be administered earlier than 6 hrs after the removal of the catheter. If traumatic puncture occurs, administration of rivaroxaban is to be delayed for 24 hrs.

Management of Bleeding Events:

Overdose of rivaroxaban may lead to hemorrhage. Discontinue rivaroxaban and initiate appropriate therapy if bleeding complications associated with overdose occur. A specific antidote for rivaroxaban is not available. Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of rivaroxaban. The use of activated charcoal to reduce absorption may be considered if the last dose ingested was within 2 hours. Due to the high plasma protein binding, rivaroxaban is not expected to be dialyzable. In mild to moderate bleeding, treatment should be supportive with fluid replacement, hemodynamic support, and blood product transfusion as needed. In cases of severe bleeding, use of procoagulant reversal agents such as prothrombin complex concentrate (PCC), activated prothrombin complex concentrate (APCC), or recombinant Factor VIIa (rFVIIa) may be considered. These, however, have not been evaluated in clinical trials. Results of a small study¹ show that prothrombin complex concentrate (PCC) appears to be an effective antidote for rivaroxaban that could be used to stop or prevent serious bleeding; however, this same study showed that PCC has no influence on dabigatran¹.

Concomitant use of other drugs affecting hemostasis increases the risk of bleeding, so in bleeding pts. secondary coagulopathy should be corrected.

Monitoring of Rivaroxaban:

Although rivaroxaban does not require routine monitoring, assays to assess the level of anticoagulation may be helpful in circumstances such as overdose in pts. with hemorrhagic or thromboembolic complications during treatment, or to assess compliance. Prothrombin time (PT) is not suitable for rivaroxaban measurement and international normalized ratio (INR) for monitoring the vitamin K antagonists cannot be applied to rivaroxaban. Anti-Factor Xa assay uses rivaroxaban containing plasma calibrators and may provide the optimal method for determining plasma rivaroxaban concentrations, such as those being developed at ITXM Diagnostics Coagulation Laboratory.

This new assay for the in vitro quantitative measurement of rivaroxaban on citrated plasma samples is a two-stage method based on the inhibition of a constant, excess amount of exogenous FXa by rivaroxaban present within the plasma sample, followed by the hydrolysis of a FXa specific chromogenic substrate of any residual remaining exogenous FXa, leading to a measurable color development at 405 nm. There is an inverse relationship between the concentration of rivaroxaban in the tested sample and color development. Increased rivaroxaban leads to increased inhibition of the excess FXa, resulting in less residual FXa available to react with the chromogenic substrate and thus, less color development occurs. The assay is calibrated using known standards containing precise amounts of rivaroxaban. This assay was designed to avoid interference of plasma factors and is insensitive to unfractionated heparins, low-molecular weight heparins, and fondaparinux. This new assay is not FDA-approved and must not be used as the sole source for diagnosis and clinical correlation is required.

Effects of Rivaroxaban on Coagulation Assays

The influence of rivaroxaban on routine coagulation tests must be recognized. Rivaroxaban can prolong PT/INR and aPTT and prolongation is concentration dependent. Mixing studies may become artificially prolonged as well. Individual factor activity clotting assays may tend to be lower, while Factor X Chromogenic testing will have a strong bias toward lower results in samples containing rivaroxaban. Occasional false positive Factor VIII Bethesda Inhibitor results may occur as shown in a recent CAP Proficiency Survey program. False positive Lupus Anticoagulant clotting assays may sometimes occur in patients on rivaroxaban. Protein C Activity and Protein S Activity clotting-based tests and Antithrombin III chromogenic methods utilizing FXa reagents may give higher results than expected, and thus there is a risk of missing patients deficient in these anticoagulation proteins when being treated with Rivaroxaban. False negative APC resistance results may occur, leading to the risk of failing to identify pts with Factor V Leiden mutations. Rivaroxaban does not normally affect immunoassays, thrombin, or reptilase time, fibrinogen or fibrinolytic assays.

REFERENCES

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