About Rivaroxaban

What is Rivaroxaban?

Rivaroxaban is the first direct oral Factor Xa Inhibitor developed to prevent and treat dangerous blood clots, with the potential to improve clinical outcomes and quality of life for a broad range of patients with, or at risk of venous and arterial thromboembolism (VAT).

Benefits of Rivaroxaban include[1]:

- Oral administration
- Rapid onset of action
- Predictable anticoagulation without need for routine coagulation monitoring or dose adjustment
- Low risk of drug-drug interactions
- No significant food interactions

How Does Rivaroxaban Work?

Rivaroxaban is an oral direct Factor Xa Inhibitor, protecting patients against blood clots by selectively targeting Factor Xa, an enzyme which acts at a key point in the blood-clotting (coagulation) process.

Coagulation requires a complex series of chemical reactions and body signals. This process of chemical reactions is often referred to as the 'Clotting Cascade'.

One of the many clotting factors (blood clot proteins) is Factor Xa that is needed to produce thrombin, which promotes the formation of blood clots. One molecule of Factor Xa catalyses the formation of approximately 1,000 thrombin molecules via what is known as a 'thrombin burst'[17,18].

Directly targeting and inhibiting Factor Xa prevents the thrombin burst, rivaroxaban inhibits thrombin generation rather than inhibiting the action of thrombin itself.

With more than 10 million patients treated* over six years across five indications in seven distinct areas of use, rivaroxaban is the most prescribed novel oral anticoagulant (OAC) in the world[1,2]

Stroke Prevention in Patients with Non-Valvular AF:

For adult patients with non-valvular atrial fibrillation (AF), once-daily rivaroxaban provides highly effective stroke prevention without the need for routine coagulation monitoring[1,3,4]. Importantly, rivaroxaban can prevent strokes without increasing the risk of heart attack and lowers the rate of most feared intracranial and fatal bleeds, compared with warfarin[1,4]. Furthermore, rivaroxaban is available in a specific dose evaluated for patients with renal impairment[1,5]. Major gastrointestinal (GI) bleeds were more common with rivaroxaban than warfarin[4]. Once-daily dosing was shown to result in significantly higher adherence and persistence compared to twice-daily treatment[6].

VTE Treatment and Prevention:

For adult patients with deep vein thrombosis (DVT) or pulmonary embolism (PE), rivaroxaban is the first novel OAC approved for acute treatment and the prevention of recurrent venous thromboembolism (VTE). As the oral, single-drug treatment, rivaroxaban 15 mg twice daily offers fast and effective blood clot regression and protection from early recurrence in the first 21 days without the need for injections or routine coagulation monitoring[1,7,8,9]. Then once-daily rivaroxaban 20 mg can provide enduring protection from the danger of DVT and/or PE recurrence[10] for as long as treatment is needed. Additionally, rivaroxaban was shown to halve the risk of major bleeding in these patients compared with the dual-drug treatment of low molecular weight heparin (LMWH) and vitamin K antagonists (VKA). Clinically relevant bleeding was comparable with dual-drug treatment[11,12].

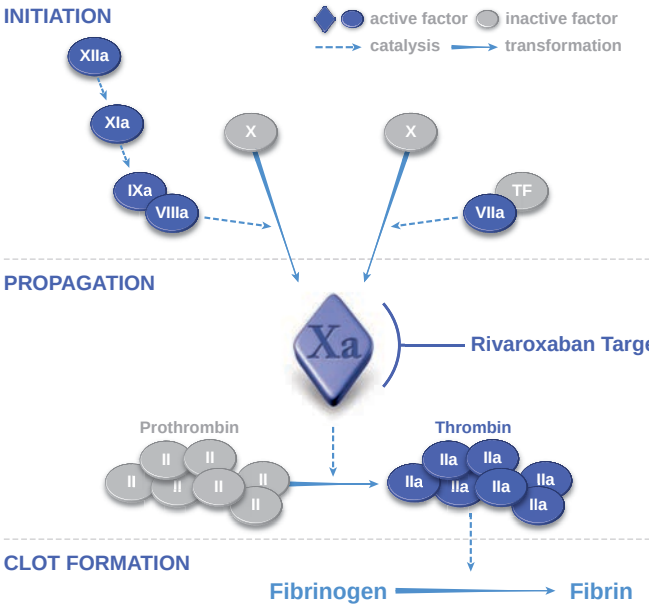
VTE Prevention in Adult Patients Following Elective Hip or Knee Replacement Surgery:

For adult patients who have had hip or knee replacement surgery, one 10 mg tablet of once-daily rivaroxaban provides superior protection against VTE with similar safety compared to the LMWH enoxaparin[13]. In real-world settings, patients on rivaroxaban were also shown to experience fewer symptomatic VTEs and similar rates of major bleeding complications post-surgery compared to older treatments[14].

Prevention of Atherothrombotic Events after an ACS in Patients with Elevated Cardiac Biomarkers***:

For patients with acute coronary syndrome (ACS), rivaroxaban 2.5 mg twice daily provides more comprehensive protection than antiplatelet therapy** alone[15]. Beyond antiplatelet therapy, rivaroxaban 2.5 mg twice daily reduces mortality and cardiovascular events without increasing the risk of fatal intracranial haemorrhage (ICH) or fatal bleeds[15,16]. However, as expected the rate of TIMI major bleeding increased with rivaroxaban 2.5 mg twice daily compared to antiplatelet therapy**[1,15,16].

Targeting Factor Xa to Inhibit Thrombin Generation



*IMS Health MIDAS, Database: Monthly Sales July 2014
**ASA alone or in combination with a thienopyridine (clopidogrel or ticlopidine)
***Patients with elevated cardiac biomarkers without prior stroke or TIA

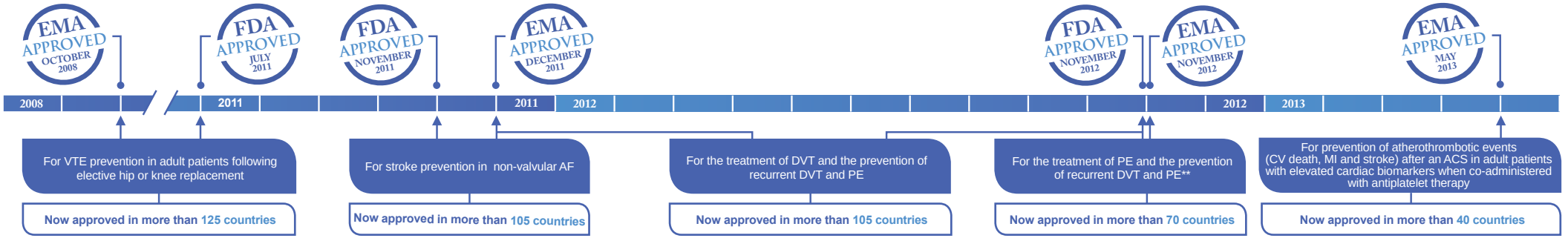
About Rivaroxaban - Continued

Rivaroxaban has demonstrated consistent clinical benefit in a broad range of acute and chronic blood-clotting conditions.Its efficacy and safety has been demonstrated in patient populations with a high number of comorbidities.

The Clinical Investigation of Rivaroxaban

The extensive evaluation of rivaroxaban to protect different patient populations at risk of venous and arterial thromboembolism (VAT) makes it the most studied novel OAC in the world. Rivaroxaban (Xarelto®) is already approved for five indications in seven areas of use and its investigation - both completed and ongoing - will include more than 275,000 patients in clinical trial and real world settings[1,2].

Rivaroxaban Regulatory Milestones



Rivaroxaban is the most broadly indicated and most prescribed novel OAC[2] and is marketed under the brand name 'Xarelto®'. Rivaroxaban was discovered by Bayer HealthCare, and is being jointly developed with Janssen Research & Development, LLC. Rivaroxaban is marketed outside the U.S. by Bayer HealthCare and in the U.S. by Janssen Pharmaceuticals, Inc. (a Johnson & Johnson Company).

Rivaroxaban Dosing

Prevention of Stroke and Systemic Embolism
in adults with non-valvular atrial fibrillation with one or more risk factors[a]

- **20 mg OD** — Patients with CrCl > 49 mL/min with food
- **OR**
- **15 mg OD** — Patients with CrCl 15 to 49 mL/min* with food

Treatment of DVT and PE…
…and extended treatment for prevention of recurrent DVT and PE in adults**

- **15 mg BID** — Patients with CrCl ≥ 15 mL/min* with food
- **AFTER 3 WEEKS TRANSITION TO**
- **20 mg OD** — Patients with CrCl ≥ 15 mL/min* with food

Prevention of VTE in adults undergoing elective hip or knee replacement

- **10 mg OD** — Patients with CrCl ≥ 15 mL/min*
- The initial dose should be taken 6 to 10 hours after surgery once haemostasis has been established

Secondary prevention in ACS in combination with standard antiplatelet therapy[b]
in adults with elevated cardiac biomarkers[c]

- **2.5 mg BID** — Patients with CrCl ≥ 15 mL/min*
- The initial dose should be taken after stabilization of the ACS event

[a]Such as congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischaemic attack; [b]ASA alone or in combination with a thienopyridine (clopidogrel or ticlopidine); [c]Troponin-I/T; creatine kinase-muscle and brain isoenzyme (CK-MB)
*Not indicated in patients with CrCl < 15 ml/min; use with caution in patients with CrCl 15-29 ml/min; **Rivaroxaban is not recommended as an alternative to unfractionated heparin in patients with PE who present hemodynamic instability or who may recieve thrombolysis or pulmonary embolectomy

To learn more, please visit https://prescribe.xarelto.com
To learn more about thrombosis, please visit www.thrombosisadviser.com

To learn more about VAT, please visit www.VATspace.com
To learn more about 'Xarelto', please visit www.xarelto.com

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