

ABOUT XARELTO®

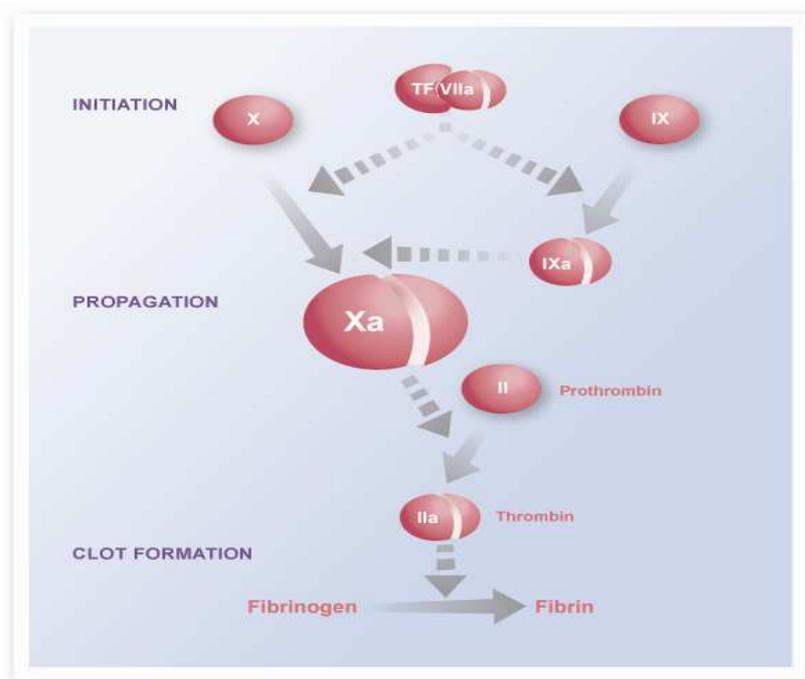
FAST FACTS

- Xarelto® (rivaroxaban) is a novel, oral direct Factor Xa inhibitor.¹ On September 30, 2008, the European Commission granted marketing approval for 'Xarelto' for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective (planned) hip or knee replacement surgery. 'Xarelto' received its first marketing approval in Canada on September 15, 2008, for the prevention of venous thromboembolic events (VTE) in patients who have undergone elective total hip or total knee replacement surgery. 'Xarelto' was submitted in July 2008 for approval to the U.S. Food and Drug Administration (FDA). On approval, Ortho-McNeil, a Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc., will market the drug in the United States. In addition to the FDA submission, filings are under review with regulatory agencies in more than 10 other countries
- 'Xarelto' is also in advanced development in a range of indications for the prevention and/or treatment of potentially deadly blood clots
- 'Xarelto' does not require injection or routine coagulation monitoring
- The extensive clinical trial program for 'Xarelto' makes it the most studied oral anticoagulant in the world today.
- 'Xarelto' was invented in Bayer's Wuppertal laboratories in Germany, and is being jointly developed by Bayer HealthCare and Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

What is 'Xarelto'?

'Xarelto' is a novel, oral direct Factor Xa inhibitor¹ in advanced development in a range of indications for the prevention and/or treatment of potentially deadly blood clots. By targeting Factor Xa at a pivotal stage in the blood-clotting process, 'Xarelto' inhibits thrombin generation rather than inhibiting the action of thrombin itself, which is important for wound healing following surgery.

Oral direct Factor Xa inhibitors, such as 'Xarelto', may also overcome disadvantages of current treatments in the outpatient setting, such as the need for regular injections or routine coagulation monitoring.



Simplified coagulation cascade

Clinical trials program

The extensive clinical trial program for 'Xarelto' makes it the most studied, oral anticoagulant in the world today. More than 60,000 patients are expected to be enrolled in the 'Xarelto' clinical development program, which will evaluate the product in the prevention and treatment of a broad range of blood-clotting disorders listed below:

- **RECORD:** VTE prevention following elective (planned) hip or knee replacement surgery (Phase III; completed)
- **MAGELLAN:** VTE prevention in medically ill patients (Phase III)
- **EINSTEIN:** VTE treatment (Phase III)
- **ROCKET AF:** Stroke prevention in patients with atrial fibrillation (Phase III)
- **ATLAS ACS TIMI 46:** Secondary prevention of acute coronary syndrome (Phase II)

For more information about the 'Xarelto' clinical development program, please refer to the "ABOUT XARELTO® CLINICAL STUDIES" backgrounder or www.clinicaltrials.gov.

RECORD trial overview

RECORD is a global program of four trials in more than 12,500 patients, comparing Xarelto® (rivaroxaban) and enoxaparin in the prevention of venous thromboembolism (VTE) after elective (planned) hip or knee replacement surgery. 'Xarelto' demonstrated superior efficacy over enoxaparin in the four RECORD trials, including head-to-head comparisons (RECORD1, 3 and 4), and a comparison of extended-duration (5 weeks) 'Xarelto' with short-duration (2 weeks) enoxaparin (RECORD2). RECORD4 was the first trial to evaluate 'Xarelto' against enoxaparin 30 mg injected subcutaneously twice-daily, which is the U.S.-approved treatment regimen for enoxaparin. In all four trials, 'Xarelto' and enoxaparin had comparable safety profiles, including low rates of major bleeding.

- In RECORD1, 'Xarelto' demonstrated a 70% relative risk reduction (RRR) in total VTE in patients undergoing total hip replacement (THR) surgery compared with enoxaparin, with a comparable safety profile including low rates of major bleeding. The duration of

thromboprophylaxis in both treatments was 35+/-4 days. Results from RECORD1 were recently published in the *New England Journal of Medicine* (2008; 358: 2765–2775)

- In RECORD2, extended-duration 'Xarelto' (35+/-4 days) demonstrated a 79% RRR in total VTE and a comparable safety profile including low rates of major bleeding in patients undergoing THR surgery compared to patients dosed with short-duration therapy with enoxaparin (12+/-2 days). Results from RECORD2 were recently published in *The Lancet* (2008; 372: 29–37)
- In RECORD3, 'Xarelto' demonstrated 49% RRR in total VTE in patients undergoing total knee replacement (TKR) surgery compared to enoxaparin, with a comparable safety profile including low rates of major bleeding. Both treatments were dosed for 12+/-2 days. Results from RECORD3 were recently published in the *New England Journal of Medicine* (2008; 358: 2776–2785)
- In RECORD4, 10 mg once-daily 'Xarelto' was compared to the U.S.-approved regimen for enoxaparin of 30 mg injected twice-daily. Xarelto demonstrated a 31.4% RRR in total VTE in patients undergoing TKR surgery compared with enoxaparin, with a comparable safety profile including low rates of major bleeding. The duration of thromboprophylaxis in both treatments was 12+/-2 days. Top-line data from RECORD4 was recently presented at European Federation of National Associations of Orthopaedics & Traumatology (EFORT), May 30, 2008

Results of a pre-specified pooled analysis of RECORD1, 2 and 3 showed that 'Xarelto' significantly reduced the composite of symptomatic VTE and all-cause mortality during the 2-week active controlled period by 56% compared with enoxaparin (0.4% versus 0.8%, respectively; odds ratio: 0.44; p<0.005) whilst maintaining a similar safety profile.^{2,3,4} These results were presented at the 20th International Congress on Thrombosis (ICT) in Athens in June 2008.

For more information about RECORD trials, including dosage and administration, please refer to the "ABOUT RECORD STUDIES" backgrounder.

Criteria for an ideal anticoagulant

Property	Benefit	Unlike
Oral administration	Convenient use both in and out of hospital in an acute and chronic setting	Parenteral drugs, such as the heparins
A predictable profile	Safe and effective regulation of coagulation from the first dose and throughout therapy	Warfarin / vitamin K antagonists
Fixed dose	No dose adjustment for majority of patients	Warfarin / vitamin K antagonists
No routine coagulation monitoring	Saves healthcare costs (fewer hospital/physician visits) and patients' time	Warfarin / vitamin K antagonists
A rapid onset and offset of action	Anticoagulation from the first dose, which stops quickly after cessation of therapy	Warfarin / vitamin K antagonists
Low risk of food and drug interactions	Hassle-free use regardless of concomitant use of other medication / diet	Warfarin / vitamin K antagonists

Regulatory filings and availability

To date, Bayer HealthCare has submitted regulatory filings in more than 10 countries, including the U.S. and China. On September 15, 2008, 'Xarelto' was approved in Canada for the prevention of venous thromboembolic events (VTE) in patients who have undergone elective total hip or knee replacement surgery. This decision marked the first approval for 'Xarelto' worldwide, and Bayer began to market the product in Canada immediately. On

September 30, 2008, the European Commission granted marketing approval for 'Xarelto' for the prevention of venous thromboembolism (VTE) in adult patients undergoing elective (planned) hip or knee replacement surgery. 'Xarelto' was submitted in July 2008 for approval to the U.S. Food and Drug Administration (FDA). On approval, Ortho-McNeil, a Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc., will market the drug in the United States.

To learn more about VTE please visit www.thrombosisadviser.com

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

References

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2. Eriksson BI. N Engl J Med 2008; 358: 2765-2775.
3. Kakkar AK. Lancet 2008; 372: 29-37.
4. Lassen MR. N Engl J Med 2008; 358: 2776-2785.