ABOUT RIVAROXABAN

FAST FACTS

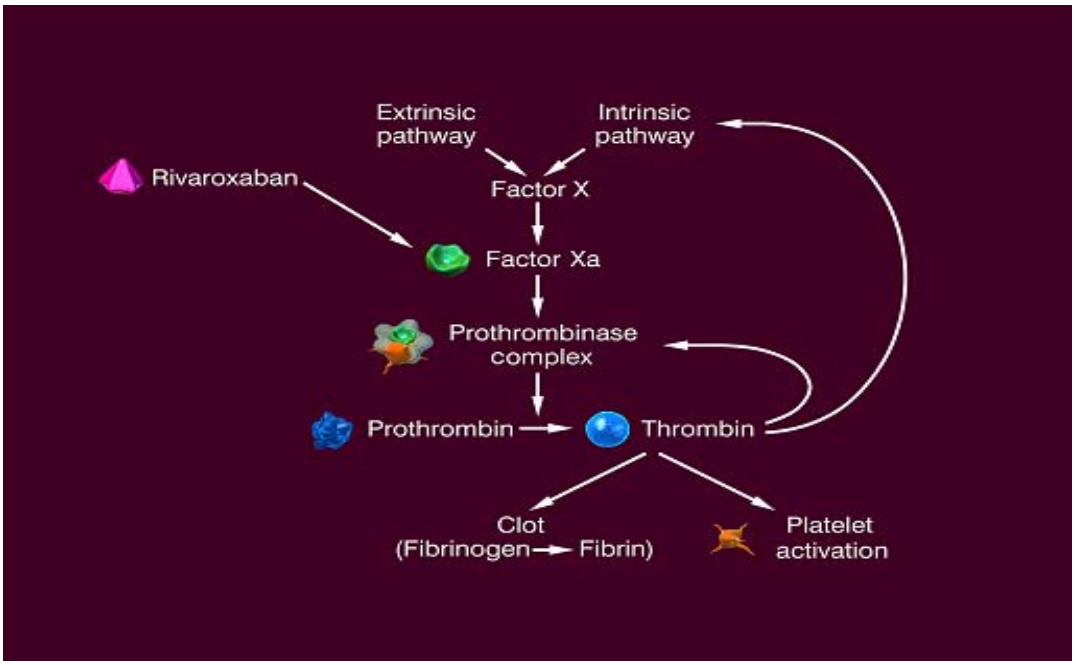
- Rivaroxaban is an oral, once-daily anticoagulant in advanced clinical development. By specifically inhibiting the action of Factor Xa, rivaroxaban targets the blood coagulation cascade at a pivotal point. Rivaroxaban also allows patients to be on the same treatment in the hospital or at home, where they may require treatment to deal with continued risk of developing life-threatening complications
- To date, rivaroxaban is the most studied oral, direct Factor Xa inhibitor in development
- Rivaroxaban is being jointly developed by Bayer HealthCare AG and Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
- Regulatory filing in the EU in October 2007, planned in the US for mid 2008

What is rivaroxaban?

Rivaroxaban is an oral, once-daily anticoagulant in advanced clinical development for patients who could benefit from the prevention of potentially deadly blood clots following major orthopedic surgery.

Rivaroxaban is a direct Factor Xa inhibitor.[1] Factor Xa has emerged as an attractive target for new anticoagulant[2] therapies due to its central point in the blood-clotting cascade. Improvements in understanding how the clotting process works suggest that Factor Xa is a pivotal enzyme to target because it carefully pinpoints a 'switch' to control the clotting process at the pivotal moment. A once-daily dose of rivaroxaban is therefore thought to act as a 'smart drug' by regulating the production of thrombin, an enzyme that promotes blood clots.[3] The targeted action of direct Factor Xa inhibitors regulates thrombin generation rather than inhibiting the action of thrombin itself. This aims to ensure that the natural clotting process, important for wound healing following surgery, can occur as intended.

Oral direct Factor Xa inhibitors also allow patients to be on the same treatment in the hospital or at home, where they may require treatment to deal with continued risk of developing life-threatening complications.



Simplified blood-clotting cascade and inhibition by Factor Xa inhibitor rivaroxaban

Clinical trials programme

To date, rivaroxaban is the most studied oral, direct Factor Xa inhibitor in development. More than 20,000 patients have been evaluated in the completed Phase II programmes and enrolled thus far in the Phase III programmes. Almost 50,000 patients are expected to be enrolled overall in the rivaroxaban clinical development programme, which will evaluate rivaroxaban in the prevention and treatment of a broad range of acute and chronic blood-clotting disorders listed below:

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

Specific information on these trials may be found on www.clinicaltrials.gov

RECORD data was presented at the 49th Annual Meeting of the American Society of Hematology (ASH) in December 2007. Data from the three distinct pivotal Phase III trials showed superior efficacy of rivaroxaban both in head-to-head comparisons with enoxaparin (RECORD1 & 3) and when comparing extended-duration (35 +/- 4 days) rivaroxaban with short-duration (10-14 days) enoxaparin followed by placebo (RECORD2). In all three trials, both rivaroxaban and enoxaparin had similar rates of major bleeding.

For more information about RECORD trials, please refer to the RECORD backgrounder

Rivaroxaban and current anticoagulants

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 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

The following table overviews the main currently available thrombosis treatments and how rivaroxaban, once approved, could help to overcome the limitations of thrombosis treatments in patients undergoing major orthopedic surgery of the lower limbs:

Drug	Position	Limitations	Rivaroxaban benefit
LMWHs e.g., enoxaparin (Lovenox)	▪ Standard treatment in the prevention and treatment of VTE ▪ Effective and safe, but with limitations	▪ Short-term use ▪ Need for injections ▪ Need to give pre-operatively according to European label	▪ Simple, convenient oral dosing regimen in and out of hospital ▪ First dose after surgery
Unfractionated heparin	▪ Effective and cheap, but inconvenient	▪ Limited to in-hospital use ▪ Weight-based dosing	▪ Simple, convenient oral dosing regimen in and out of hospital ▪ No dose adjustment for weight, gender or age
Vitamin K antagonists e.g., warfarin	▪ Widely used oral anticoagulant	▪ Frequent monitoring/dose adjustments/difficulty to maintain therapeutic range for many patients ▪ Food and drug interactions	▪ Predictable, simple, convenient ▪ Fast onset of action
Fondaparinux (Arixtra)	▪ Demonstrates that Factor Xa is an attractive target for inhibition	▪ Need for injections	▪ Simple, convenient oral dosing regimen in and out of hospital
Dabigatran (Pradaxa)	▪ Oral, convenient, no need for monitoring	▪ Dabigatran was demonstrated to be as effective and safe as injectable enoxaparin in preventing VTE and all cause mortality following total hip and knee replacement surgery	▪ Superior efficacy of rivaroxaban both in head-to-head comparisons with enoxaparin (RECORD1 & 3) and when comparing extended-duration rivaroxaban with short-duration enoxaparin (RECORD2)

Rivaroxaban is being jointly developed by Bayer HealthCare AG and Johnson & Johnson Pharmaceutical Research & Development, L.L.C. Bayer HealthCare submitted a regulatory filing to the European Agency for the Evaluation of Medicinal Products (EMEA) at the end of October 2007 for approval to market rivaroxaban in the EU for the prevention of VTE in patients undergoing major orthopedic surgery of the lower limbs. Upon regulatory approval, rivaroxaban will be commercialised in Europe by Bayer Schering Pharma. A filing for rivaroxaban for a similar indication in the United States is planned in mid 2008.

References

1. Perzborn E. J Thromb Haemost 2005; 3: 514-21.
2. Eriksson BI. J Thromb Haemost 2006; 4: 121-8.
3. Turpie AG. J Thromb Haemost 2005; 3: 2479-86.