Pharmacotherapeutic report, summary

Rivaroxaban (Xarelto®) for the indication 'treatment of pulmonary embolism'
Recommendation by Zorginstituut Nederland dated 25 November 2013, based on an evaluation by the WAR (Scientific Advisory Committee)

The WAR has approved a pharmacotherapeutic report for the medicine rivaroxaban (Xarelto®) 15 mg tablet for oral use. In determining its therapeutic value, it was compared with enoxaparin (a low molecular weight heparin) in combination with warfarin or acenocoumarol (vitamin K antagonists). They reached the following conclusion.

- the therapeutic value of rivaroxaban for the treatment of pulmonary embolism in adults is equivalent to that of enoxaparin/acenocoumarol.

Medicine. Rivaroxaban [15 mg and 20 mg tablets for oral use]

Registered indication. "Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and prevention of recurrent DVT and PE in adults". In 2012 this was: 'Treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT and pulmonary embolism after an acute DVT in adults'.

Rivaroxaban is also registered for:

- 15 mg and 20 mg tablets: 'Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack.'
- 10 mg tablet: 'Prevention of venous thromboembolism in adult patients undergoing elective hip or knee replacement surgery' and
- 2.5 mg tablet: Xarelto, co-administered with acetylsalicylic acid (ASA) alone or with ASA plus clopidogrel or ticlopidine, is indicated for the prevention of atherothrombotic events in adult patients after an acute coronary syndrome (ACS) with elevated cardiac biomarkers

Posology. 15 mg twice daily during the first three weeks, followed by 20 mg once daily.

Mechanism of action. Rivaroxaban is a highly selective direct factor Xa inhibitor with oral bioavailability. Inhibition of factor Xa interrupts the intrinsic and extrinsic pathway of the blood coagulation cascade, inhibiting both thrombin formation and development of thrombi. Rivaroxaban does not inhibit thrombin (activated Factor II) and no effects on platelets have been demonstrated.

Specific details. This assessment relates to the partial indication treatment of pulmonary embolism. See the report from 2012 for the assessment of rivaroxaban for 'Treatment of deep vein thrombosis (DVT) and prevention of recurrent DVT and pulmonary embolism after an acute DVT in adults' and for 'Prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior stroke or transient ischaemic attack'. Rivaroxaban for the prevention of VTE after elective hip or knee surgery was assessed in 2009 (CFH report 09/03).

Summary of the therapeutic value

Intended effects. In an open label, randomised phase 3 study of the treatment of pulmonary embolism, rivaroxaban was non-inferior in respect of the primary efficacy outcome –symptomatic recurrent venous thromboembolism (deep vein thrombosis or pulmonary embolism) – to 8 days' treatment with enoxaparin followed by or overlapping with warfarin or acenocoumarol based on the INR (hazard ratio 1.12 [0.75-1.68]; 0.003). Superiority in comparison with the standard treatment has not been demonstrated (p=0.57).
Unintended effects. A pooled analysis of EINSTEIN-DVT and EINSTEIN-PE showed that the incidence rates for the primary safety outcome (major or clinically relevant non-major bleeding events) as well as the secondary safety outcome (major bleeding events) were similar for both rivaroxaban and enoxaparin/VKA. The incidence of major bleeding in the pooled comparison and in EINSTEIN-PE was significantly lower with rivaroxaban than with enoxaparin/acenocoumarol. A difference seems to exist in the location of bleedings: the incidence of intracranial bleedings may be lower with rivaroxaban (not statistically tested), while a meta-analysis showed that the incidence of gastrointestinal haemorrhages was higher with rivaroxaban than with the standard treatment. However, this did not lead to a difference in mortality.
Experience. Experience with rivaroxaban is limited for the pulmonary embolism indication, while ample experience has been gained with enoxaparin and the vitamin K antagonists.
Applicability. There are no major differences in applicability between rivaroxaban, enoxaparin, acenocoumarol and phenprocoumon. However, a specific antidote antagonising the pharmacodynamic effect of rivaroxaban is not available.
Ease of use. The ease of use of rivaroxaban is greater than that of enoxaparin due to its oral administration, and greater than that of phenprocoumon and acenocoumarol because the doses of vitamin K antagonists are based on the INR. This is an advantage for the patient and his/her physician. However, there is no evidence that this improved ease of use leads to improved treatment outcomes.

Final conclusion on therapeutic value.
The superiority of rivaroxaban over the standard treatment has not been demonstrated. The incidence of adverse reactions to treatment with rivaroxaban is similar to that with the standard treatment. There may be differences in the location of bleeding, possibly with fewer intracranial and more gastrointestinal haemorrhages with rivaroxaban than with the standard therapy. The therapeutic value of rivaroxaban for the treatment of pulmonary embolism in adults is equal to that of enoxaparin/acenocoumarol.

For further information, please contact: MLinden@zinl.nl; warcg@zinl.nl

Furthermore, Zorginstituut Nederland points out that only the summary of this report was translated. A proper understanding of all relevant considerations and facts would require familiarity with the Dutch version of this report, including all appendices.