Pharmacotherapeutic report, summary

Rivaroxaban (Xarelto®) for the indication 'Prevention of CVA and systemic embolism in patients with non-valvular atrium fibrillation'

Approved on 26 October 2012 by the Medicinal Products Reimbursement Committee (CFH)

Medicine. Rivaroxaban (Xarelto®) 20 mg tablet

Registered indication. "Prevention of cerebrovascular accident (CVA) and systemic embolism in adult patients with non-valvular atrium fibrillation with one or more risk factors, such as congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, prior CVA or TIA (transient ischaemic attack)."

Posology. 20 mg 1x/day orally.

Mechanism of action. Rivaroxaban is a selective, direct factor Xa-inhibitor. Inhibition of factor Xa interrupts both the intrinsic and the extrinsic pathway of the blood coagulation cascade, resulting in inhibition of both thrombin formation and development of thrombi.

Specific details. In 2011 rivaroxaban was registered, together with the indication under discussion, for the treatment of deep vein thrombosis (DVT) and the prevention of both recurrent DVT and pulmonary embolism following an acute DVT in adults. These indications have been assessed in a separate report.

Previously (in 2009) rivaroxaban was assessed for the indication: Prevention of venous thromboembolism in adult patients undergoing hip or knee replacement surgery (CFH-report 09/03).

Summary of the therapeutic value

Intended effects. In a direct comparison with warfarin, rivaroxaban was noninferior to warfarin. Superiority in comparison with warfarin was demonstrated in the per-protocol analysis, but not in the more appropriate ITT analysis. In a direct comparison, the comparative treatment dabigatran 150 mg 2x/day was superior to warfarin in the ITT analysis. The lower dose of 110 mg dabigatran 2x/day is non-inferior. No difference in efficacy could be proven in an indirect comparison of rivaroxaban and dabigatran, as a result of differences in patient population and study design of the two phase 3 studies.

Unintended effects. In a direct comparison, the incidence of major and clinically relevant non-major bleedings was comparable for rivaroxaban and warfarin. However, the incidence of critical bleeding, intracranial hemorrhage and fatal bleeding was significantly lower in the rivaroxaban group. Gastrointestinal adverse reactions were more frequent during treatment with rivaroxaban. In an indirect comparison between rivaroxaban and dabigatran, gastrointestinal haemorrhages occurred more frequently with both drugs than in patients treated with warfarin, but there was significantly less intracranial bleeding and fatal bleeding/life-threatening haemorrhages with both rivaroxaban and dabigatran than with warfarin. The reduction of intracranial hemorrhage is of potential interest due to the bad prognosis of these patients.

Experience. Experience with rivaroxaban and dabigatran for the indication atrium fibrillation is limited, while ample experience has been gained with acenocoumarol and phenprocoumon.
Applicability. There are no major differences in the applicability of rivaroxaban, dabigatran, acenocoumarol and phenprocoumon. However, the interactions with other medicinal products of rivaroxaban and dabigatran are more favourable than those of the vitamin K antagonists.
Ease of use. Ease of use of rivaroxaban and dabigatran is greater than that of phenprocoumon and acenocoumarol, because the dose of vitamin K antagonists is based on the INR. However, the regularity of INR checks with vitamin K antagonists could be an advantage that increases therapy compliance.
Final conclusion. In comparison with vitamin K antagonists, rivaroxaban has a therapeutic added value and its therapeutic value is equal to that of dabigatran in the prevention of CVA and systemic embolism in adult patients with non-valvular atrium fibrillation with one ore more risk factors.