New Drug Review

Rivaroxaban: An Oral Factor Xa Inhibitor

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ABSTRACT

Background: Currently available anticoagulants utilized for venous thromboembolism (VTE) treatment and prevention and stroke prevention in patients with atrial fibrillation (AF) have proven effectiveness but are not optimally utilized because of barriers such as the need for subcutaneous administration and requisite routine laboratory monitoring. Rivaroxaban, a novel oral Xa inhibitor, is an alternative to standard therapies utilized for VTE prevention after elective orthopedic surgery, primary and secondary stroke prevention in nonvalvular AF, VTE treatment after an acute VTE event, and secondary prevention after the acute coronary syndromes (ACS).

Objective: This article reviews the pharmacology, efficacy, and tolerability of rivaroxaban for VTE prophylaxis in post–orthopedic surgery and medically ill patients, stroke prevention in nonvalvular AF, adjunctive therapy in patients with ACS, and VTE treatment.

Methods: International Pharmaceutical Abstracts and EMBASE were searched for English-only clinical trials and reviews published between 1970 and March 15, 2012. PubMed was searched for articles published between 1970 and June 30, 2012. Additional trials and reviews were identified from the citations of published articles.

Results: Eighty-nine publications were identified: 10 clinical trials and 1 meta-analysis were used to obtain efficacy and tolerability data, and 1 analysis of pooled data from the clinical trials was included; 17 pharmacokinetic, pharmacodynamic, and drug–drug interaction studies were included; and 5 cost-analyses were reviewed. These data showed rivaroxaban to be noninferior to enoxaparin for thromboprophylaxis of VTE after total knee and total hip replacement surgery. It was also shown to be noninferior to vitamin K antagonist therapy for primary and recurrent stroke prevention in nonvalvular AF as well as for the treatment of VTE after an acute deep vein thrombosis or pulmonary embolism. It also showed benefit in lowering the risk for major adverse cardiovascular events after ACS. Differences in major bleeding rates were not statistically significant between rivaroxaban and comparators across the various studies, with the exception of ACS, in which there were higher rates of non–coronary artery bypass graft surgery related bleeding and intracranial hemorrhage.

Conclusions: Based on the findings of the studies reported in this review, rivaroxaban is an effective option for the prevention of VTE after orthopedic surgery, stroke prevention for nonvalvular AF, and treatment of VTE. At this time, rivaroxaban cannot be recommended for secondary risk reduction after ACS because of the increased bleeding risk. (*Clin Ther*. 2013;35:4–27) © 2013 Published by Elsevier HS Journals, Inc.

Key words: anticoagulants, rivaroxaban, venous thromboembolism treatment, venous thromboembolism prophylaxis, atrial fibrillation thromboembolism prophylaxis

INTRODUCTION

For many decades, vitamin K antagonists (VKAs) have been the only oral anticoagulants available for the primary and secondary prevention of venous and arterial thromboembolic events. VKAs have been shown to be highly effective in many settings and are now used by millions of patients worldwide.[1] Despite their efficacy, the management of VKAs is challenging due to their complex pharmacokinetic and pharmacodynamic properties and narrow therapeutic range. Additional limitations to the use of VKAs include their slow onset and offset of action, multiple drug and dietary interactions, and need for frequent monitoring to maintain therapeutic range.[2] To overcome the limitations of

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VKAs, the development of new oral anticoagulants has aimed to find effective treatment options that are more tolerable and more convenient. Among these new classes of anticoagulants are the oral direct thrombin inhibitors (DTIs) and the direct factor Xa inhibitors.

Rivaroxaban is approved by the US Food and Drug Administration (FDA), European Medicines Agency (EMA), and Health Canada for the reduction of the risk for stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF).[3–5] Rivaroxaban also has approval by the FDA, EMA, and Health Canada for the prevention of venous thromboembolism (VTE) in patients undergoing total knee or hip replacement surgery.[3,5,6] Rivaroxaban has additional approval by Health Canada for treatment of deep vein thrombosis (DVT) without symptomatic pulmonary embolism (PE).[7] The FDA and EMA have approved rivaroxaban for the treatment of DVT and PE and for the reduction in the risk for recurrence of DVT and PE.[3,8]

MATERIALS AND METHODS

PubMed, EMBASE, and International Pharmaceutical Abstracts were searched using the search term *rivaroxaban*. Only English-language clinical trials and systematic reviews published between 1970 and March 15, 2012, and additional trials and reviews referenced in published articles were included. PubMed was searched for studies published between 1970 and June 30, 2012. In addition, cost analyses were identified by searching the terms *rivaroxaban* and *cost analysis* in PubMed.

RESULTS

Eighty-nine publications were identified: 10 clinical trials and 1 meta-analysis were used to obtain efficacy and tolerability data, and 1 analysis of pooled data from the clinical trials were included; 17 pharmacokinetic, pharmacodynamic, and drug–drug interaction studies were included; and 5 cost analyses were reviewed.

Mechanism of Action

VKAs, such as warfarin, produce their anticoagulant effect by targeting the vitamin K conversion cycle and inhibiting vitamin K epoxide reductase (VKOR). Inhibition of this cycle causes hepatic production of coagulation factors (II, VII, IX, and X) with reduced procoagulant activity. In addition to their anticoagulant effect, VKAs inhibit regulatory anticoagulant proteins C and S and therefore have the potential to exert procoagulant effects.[1] Oral direct factor Xa inhibitors, such as rivaroxaban, selectively block the active site of factor Xa.[3] They not only inhibit free factor Xa but also prothrombinase activity and clot-associated factor Xa.[9] This mechanism is unique to small, direct inhibitors because factor Xa that is incorporated in the prothrombinase complex is protected from inhibition by antithrombin and by antithrombin-dependent anticoagulants.[1] Rivaroxaban and other factor Xa inhibitors also inhibit thrombin generation.[10]

Pharmacodynamic and Pharmacokinetic Properties of Rivaroxaban

Rivaroxaban is metabolized in the liver through oxidative and hydrolytic processes catalyzed by cytochrome P450 (CYP) 3A4/5 and 2J2. Rivaroxaban is also a substrate for the P-glycoprotein (P-gp) efflux transporter protein.[3] Approximately 66% of rivaroxaban is excreted in the kidneys (36% as unchanged drug), and the remainder is excreted in the feces as unchanged drug.[11]

Healthy Subjects

In healthy white men aged 19 to 45 years, the administration of a single dose of rivaroxaban 5 to 80 mg resulted in a maximum factor Xa inhibition of 20% to 80% within 1 to 4 hours after administration. After administration of the oral tablets, T_{max} was 2 hours and $t_{1/2}$ was between 6 and 7 hours. Rivaroxaban prolonged the prothrombin time (PT), activated partial thromboplastin time (aPTT), and HepTest (a low-molecular-weight heparin [LMWH] activity assay) but had no effect on thrombin or antithrombin activity.[12] A study that administered multiple doses of rivaroxaban ranging from 5 mg once or twice daily to 30 mg twice daily to healthy men aged 20 to 45 years found that T_{max} was 2 to 4 hours and maximum factor Xa inhibition ranged from 22% (5-mg dose) to 68% (30-mg dose). Similar to the single-dose study, PT, aPTT, and HepTest were prolonged and reached maximum levels after 1 to 4 hours and the $t_{1/2}$ was 5.7 to 9.2 hours at steady state.[13] An analysis of data from the multiple-dose study found that rivaroxaban has predictable, dose-proportional pharmacokinetic (PK) and pharmacodynamic (PD) properties.[14] Similar PK and PD parameters were found in healthy Chinese subjects.[15] See **Table I**[4,11,12,16] for a summary of the characteristics of rivaroxaban in healthy subjects.

Elderly Subjects

The AUC of rivaroxaban is increased by 50% and the $t_{1/2}$ prolonged to between 11 and 13 hours in elderly patients