**Product Information1,2,3**

**Product description**

Rivaroxaban (Xarelto) is a factor Xa inhibitor and is available as tablets in the following strengths: 10mg, 15mg, and 20mg. The national drug code for all of the formulations are 50458-0578-30, 50458-0579-30, 50458-580 -30. The Veterans Affairs contract price for rivaroxaban is $2,380.00 per patient per year. Rivaroxaban is classified as direct factor Xa inhibitor under the American Hospital Formulary Service

(AHFS).

**Indications**

Rivaroxaban is approved for prophylaxis of Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) in patients undergoing knee or hip surgery, reduction in risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (NVAF) in the United States. In Canada, it is also approved for treatment of DVT without symptomatic PE.

**Pharmacokinetics**

Rivaroxaban is administered by mouth and has a Cmax of 2-4 hours after administration. Rivaroxaban is metabolized hepatically via CYP3A4/5 and CYP2J2. Rivaroxaban is eliminated in the urine, where 66% is primarily by active tubular secretion, of which 36% as unchanged drug and 30% as inactive metabolites. 28% is also eliminated in the feces, of which 7% as unchanged drug and 21% as inactive metabolites. The half-life of rivaroxaban is 5-9 hours in healthy patients ages 20-45 years old.

**Pharmacodynamics**

Rivaroxaban is a factor Xa inhibitor that is orally bioavailable. Rivaroxaban selectively blocks factor Xa and does not require a cofactor for activity. Blocking factor Xa results in inhibition of platelet activation and fibrin clot formation.

**Contraindications**

Rivaroxaban is contraindicated in active pathological bleeding and severe hypersensitivity reaction to rivaroxaban.

**Warnings/Precautions**  
Rivaroxaban has an increased risk of bleeding and can cause serious or fatal bleeding. Do not administer rivaroxaban in patients with active pathological hemorrhage or in patients who have a history of severe hypersensitivity reactions to rivaroxaban. If rivaroxaban is discontinued in NVAF, there is an increased risk of stroke. Consider adding another anticoagulant if rivaroxaban is discontinued.

If patients are treated with rivaroxaban to prevent thromboembolic complications during neuraxial anesthesia or spinal puncture, patients are at risk in developing an epidural or spinal hematoma. This can lead to long-term or permanent paralysis. The epidural catheter my removed after 18 hours after the last administration of rivaroxaban. The next rivaroxaban dose can be administered 6 hours after the removal of the catheter. If traumatic puncture occurs, delayed the administration of Rivaroxaban for 24 hours.

Rivaroxaban is in pregnancy category C: Rivaroxaban has a risk of pregnancy- related hemorrhage and should be used in caution in pregnant women. Rivaroxaban should only be used if the benefits outweigh the risks to the mother and fetus.

Adverse effects reported from the study Rocket-AF showed that bleeding was the most common. Major bleeding was reported in 5.6% of patients, 1.3% had bleeding into a critical organ, 0.4% had fatal bleeding, 2.6% had bleeding resulting in transfusion of greater than equal to 2 units of whole blood or packed red blood cells, and 3.1% had gastrointestinal bleeding.   
  
**Drug interactions**   
Rivaroxaban is a major substrate of CYP3A4/5, P-glycoprotein (P-Gp), and ATP- binding cassette G2 transporters (ABCG2). Rivaroxaban should not be administered with P-Gp inhibitors and strong CYP3A4 inhibitors (ketoconazole, itraconazole, lopinavir/ritonavir, ritonavir, indinavir/ritonavir, and conivaptan), NSAIDS, and aspirin because it may increase bleeding risk.

Rivaroxaban should not be administered with drugs that are P-Gp inducers and strong CYP3A4 inducers (carbamazepine, phenytoin, rifampin, St. John’s wort) because they may decrease the effect of rivaroxaban.

Rivaroxaban should be avoided in combination with other anticoagulation and antiplatelet medications due to enhancement of anticoagulation effects. Rivaroxaban should also be avoided with grapefruit juice because it may increase levels and effects of Rivaroxaban.   
Rivaroxaban should be avoided in patients with renal impairment in NVAF with creatinine clearance (CrCl) < 15 mL/min. If used for DVT prophylaxis, avoid in patients with Crcl<30 mL/min and use with caution in moderate impairment (CrCl 30 to <50 mL/min).  
  
**Dosing and Administration**  
The recommended dose for nonvalvular atrial fibrillation is 20 mg once daily with the evening meal taken orally for patients with CrCl >50 mL/min. For patients with CrCl 15-50 mL/min, the recommended dose is 15 mg once daily with the evening meal. The recommended dose for DVT prophylaxis is 10 mg taken orally once daily with or without food. The initial dose should be taken 6 to 10 hours after surgery once hemostasis has been established. The treatment duration is 35 days for patients who have had hip replacement surgery and is 12 days for patients who have had knee replacement surgery. Rivaroxaban is a new drug to mark and is easily accessible. If switching from warfarin, start rivaroxaban when the International Normalized Ratio (INR) is below 3.0 to avoid inadequate anticoagulation.

**Disease description4**

Atrial Fibrillation (AF) is the most common form of sustained cardiac arrhythmia. Patients with AF have a 5-fold increase in risk of ischemic stroke. The use of oral antithrombotic reduces this risk.

**Epidemiology and risk factors**

One in four Americans over the age of 40 will develop AF in their lifetime. It is estimated that by 2050, over 16 million Americans will be diagnosed with AF. Risk factors for developing AF include age, heart disease, other chronic conditions, high blood pressure, drinking alcohol, and family history.

The risk factors for patients with AF developing a stroke include congestive heart failure, hypertension, age >75 years old, diabetes mellitus, and previous stroke or transient ischemic attack. Risk factors for developing a stroke in patients with AF can be calculated by using the CHADS2 score.

**Pathophysiology**

Patients with AF have a continuous rapid firing of multiple atrial foci. The AV node fails to act as a gate keeper and has uncoordinated atrial activation. The risk of stroke in patients with AF is due to blood stasis in the left atrial appendage of the heart.

**Clinical presentation**

Most patients with AF present as asymptomatic or may present with a decreased cardiac output secondary to loss of atrial systole and decreased ventricular filling time. Symptoms such as hypotension, dyspnea, fatigue, lightheadedness, syncope, or angina may or may not be present in patients with AF.

**Economic Burden**

According to the American Heart Association, the total cost burden of AF is $26 billion.

**Treatment Approaches**

Stroke prophylaxis in patients with AF is treated with antithrombotic agents. These agents include Vitamin K antagonists (warfarin), antiplatelet agents (aspirin, clopidogrel), heparins, factor Xa inhibitors, and direct thrombin inhibitors. Choice of agent is dependent on risk of stroke in AF patients dependent on the CHADS2 score. According to the CHEST Guidelines, patients with AF with a CHADS2 score of 0, or very low risk of stroke, the guidelines recommend no therapy. If therapy should be elected for stroke prophylaxis, the guidelines recommend aspirin 75mg to 325mg daily rather than oral anticoagulation or combination therapy with aspirin and clopidogrel. For patients with AF with a CHADS2 score of 1, or an intermediate risk of stroke, the guidelines recommend oral anticoagulation. For patients with AF who are at a high risk of stroke, CHADS2 score of 2 or more, oral anticoagulation is recommended by the guidelines. If oral anticoagulation is not suitable due to patient characteristics in CHADS2 score >1, combination therapy with aspirin and clopidogrel is recommended. The newly updated 2012 CHEST Guidelines at this point recommend patients with a CHADS2 score >1 use dabigatran 150mg twice daily over adjusted-dose VKA therapy (INR range 2-3). Specific exclusions apply. For patients with AF with mitral stenosis or patients with AF with stable CAD, the updated guidelines recommend the use of an adjusted-dose VKA therapy (INR range 2-3) over dabigatran 150mg twice daily.

At this time, the updated 2012 CHEST Guidelines do not comment on the where rivaroxaban fits into therapy. However, as it is an oral anticoagulant that acts at the Xa factor in the coagulation cascade, it would be suggested that it could be a therapeutic alternative to dabigatran. Because this is a new FDA approved indication for stroke prophylaxis in patients with AF as of November 2011, the CHEST guidelines published in February 2012 was unable to assess its place in therapy.

**Therapy Outcomes**

The therapy outcome of rivaroxaban or the use of anticoagulants in patients with atrial fibrillation is to reduce the risk of stroke in patients with nonvalvular atrial fibrillation.At this time, current practice and use of rivaroxaban matches up with current literature with the use of rivaroxaban in stroke prophylaxis in patients with AF. Practitioners are unsure of its use for this recently approved FDA indication and CHEST guidelines currently do not mention its use.

**Supporting Clinical Evidence3**

**Literature Search**

Using the search terms “rivaroxaban” and “warfarin”, Medline came up with 122 results consisting of mostly reviews from the ROCKET-AF trial.

**ROCKET AF**

With help from the results of the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibitor Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF), Xarelto was FDA approved for stroke prevention in 2011. The objective of the ROCKET AF trial was to compare the efficacy of rivaroxaban versus warfarin at preventing stroke in patients with nonvalvular atrial fibrillation. It was conducted at 1178 participating sites in 45 countries. Randomization occurred from December 18, 2006, through June 17, 2009 and the study was terminated on May 28, 2010. The trial design was a multicenter, randomized, double-blind, double-dummy, event-driven trial. Patients in each group received a placebo tablet in order to maintain blinding. Randomization was performed with the use of a central 24-hour, computerized, automated voice-response system. ROCKET AF had an extensive inclusion and exclusion criteria. All patients had to have atrial fibrillation recently documented with a history of stroke. Patients were not eligible with certain bleeding histories. The complete list of inclusion and exclusion criteria is found below.

**Inclusion criteria**

Men or women aged ≥18 years with non-valvular atrial fibrillation; Atrial fibrillation must be documented by ECG evidence within 30 days before randomization. In addition, subjects must have medical evidence of atrial fibrillation within 1 year before and at least one day before the qualifying ECG evidence; patient has history of prior ischemic stroke, TIA or non-CNS systemic embolism believed to be cardioembolic in origin or has 2 or more of the following risk factors: Heart failure and/or left ventricular ejection fraction ≤35%, hypertension (defined as use of antihypertensive medications within 6 months before the screening visit or persistent systolic blood pressure above 140 mmHg or diastolic blood pressure

above 90 mmHg), age ≥75 years, diabetes mellitus (defined as a history of type 1 or type 2 diabetes mellitus or use of antidiabetic medications within 6 months before screening visit)

**Exclusion criteria**

Patients were excluded based on certain cardiac related conditions including hemodynamically significant mitral valve stenosis, prosthetic heart valve (annuloplasty with or without prosthetic ring, commissurotomy and/or valvuloplasty are permitted), planned cardioversion (electrical or pharmacological), transient atrial fibrillation caused by a reversible disorder (e.g., thyrotoxicosis, PE, recent surgery, MI), known presence of atrial myxoma or left ventricular thrombus, active endocarditis. Patients were also excluded if they met Hemorrhage Risk-Related Criteria which includes active internal bleeding, history of or condition associated with increased bleeding risk including, but not limited to major surgical procedure or trauma within 30 days before the randomization visit, clinically significant gastrointestinal bleeding within 6 months before the randomization visit, history of intracranial, intraocular, spinal, or atraumatic intra-articular bleeding, chronic hemorrhagic disorder, known intracranial neoplasm, arteriovenous malformation, or aneurysm. In addition, those with planned invasive procedure with potential for uncontrolled bleeding, including major surgery, platelet count <90,000/μL at the screening visit, sustained uncontrolled hypertension: systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥100 mmHg

Certain conditions and medication therapies also excluded patients from entering the study. For example, those with a severe, disabling stroke (modified Rankin score of 4 to 5, inclusive) within 3 months or any stroke within 14 days before the randomization visit, transient ischemic attack within 3 days before the randomization visit, indication for anticoagulant therapy for a condition other than atrial fibrillation (e.g., VTE), anemia (hemoglobin <10 g/dL) at the screening visit, pregnancy or breast-feeding, any other contraindication to warfarin, known HIV infection at time of screening, calculated CLCR <30 mL/min at the screening visit (refer to Attachment 4 for calculating CLCR), known significant liver disease (e.g., acute clinical hepatitis, chronic active hepatitis, cirrhosis), or ALT >3x the ULN were not permitted. Treatment with aspirin (>100 mg daily), aspirin in combination with thienopyridines within 5 days before randomization, intravenous antiplatelets within 5 days before randomization, fibrinolytics within 10 days before randomization, anticipated need for chronic treatment with a non-steroidal anti-inflammatory drug, systemic treatment with a strong inhibitor of cytochrome P450 3A4, such as ketoconazole or protease inhibitors, within 4 days before randomization, or planned treatment during the time period of the study, pr a strong inducer of cytochrome P450 3A4, such as rifampin/rifampicin, within 4 days before randomization, or planned treatment during the time period of the study were not included.

**Results**

The study population of ROCKET AF consisted of patients at moderate to high risk of stroke based on CHADS2 score of equal to or greater than 2. The majority of patients were male at 60% and most patients were white at 83%. A total of 14,264 patients were randomized a practice sites all around the world with 38% coming from central Europe. Only 32 patients were lost to follow-up and another 93 patients (50 in the rivaroxaban group and 43 in the warfarin group) were excluded from efficacy analysis before unblinding due to violations of Good Clinical Practice guidelines at one particular site. Patients were randomly assigned to receive 20 mg rivaroxaban daily (or 15 mg daily in those with a creatinine clearance of 30 - 49 ml per minute) or adjusted-dose warfarin with a target INR of 2.0 - 3.0. Primary outcomes included stroke or non-CNS systemic embolism. Secondary outcomes included major and nonmajor bleeding, myocardial infarction, and death. Stroke or systemic embolism occurred in 188 patients in the rivaroxaban group (1.7% per year) and in 241 patients in the warfarin group (2.2% per year). Major and clinically relevant nonmajor bleeding occurred in 1475 patients (14.9%) in the rivaroxaban group and in 1449 patients (14.5%) in the warfarin group. During treatment, myocardial infarction occurred in 101 patients (0.9%) in the rivaroxaban group and in 126 patients (1.1%) in the warfarin group, and there were 208 deaths (1.9%) in the rivaroxaban group and 250 deaths (2.2%) in the warfarin group. A minimum of 363 events would provide a power of 95% to calculate a noninferiority margin of 1.46 with a one-sided alpha level of 0.025. Therefore, 405 events were selected as the prespecified target to ensure a robust statistical result. The authors projected an event rate of 2.3% per 100 patient-years in the warfarin group and a projected 14% rate of annual attrition, so they estimated that approximately 14,000 patients would need to be randomly assigned to a study group.

The primary analysis of the study determined that rivaroxaban was non-inferior to warfarin in patients with atrial fibrillation for the prevention of stroke and systemic embolism. There were no significant differences in the risk of major bleeding, although intracranial and fatal bleeding occurred less frequently in the rivaroxaban group. The study population consisted of multiple geographical areas and consisted of an elderly population with creatinine clearance greater than 30 ml per minute. Caution should be made in generalizing these results to younger patients and those with renal failure. One important limitation to note is that warfarin was in therapeutic range only 55% of the time which may have favored rivaroxaban in the results. The study was also relatively short with a median treatment exposure of 590 days and 1 site violated good clinical practice guidelines. Finally, ROCKET AF was funded by Johnson & Johnson and Bayer.

**Supporting Economic Evidence**

PubMed/Medline (EbscoHost)

rivaroxaban and cost\* (41 results)

rivaroxaban and econ\* (24 results)

rivaroxaban and budget (0 results)

Limits: English language

Rivaroxaban has recently been FDA approved for stroke prophylaxis in patients with non-valvular atrial fibrillation in November 2011. At this time, no economic literature has currently been published assessing the economic results of the use of rivaroxaban for stroke prophylaxis in patients with non-valvular atrial fibrillation. All current published economic literature pertains to another FDA approved indication of rivaroxaban in the use of venous thromboembolism prevention in patients post hip or knee surgery. The authors of this drug monograph will continue to monitor the literature for any updates as they become available.

**Budget Impact Analysis**5,6,7,8,9

Our Budget Impact Analysis took the perspective of the Veterans Affairs hospital system for the 2011 fiscal year; our time horizon was therefore 12 months. Rivaroxaban 20 mg daily, dabigatran 150 mg twice daily, and warfarin (titrated to INR of 2-3) were evaluated in this analysis, although dabigatran and warfarin were not compared directly (as CHEST guidelines consider both options appropriate in atrial fibrillation). Our population was based on the estimated number of VA patients treated for atrial fibrillation in FY 2011 (per the VARIA trial, 2011). Budget costs were confined to medication costs, INR monitoring (where applicable), and cost of serious adverse events. Three scenarios were evaluated in which all patients with NVAF were treated with one of the following: warfarin, dabigatran, or rivaroxaban. Drug costs were taken from federal contract prices, and monitoring/ADE costs were taken from available relevant economic sources.

Our economic analysis determined the yearly cost of treating this population with rivaroxaban to be $222.2 million, as compared to $59.3 million for warfarin and $181.9 million with dabigatran. Drug costs were taken from federal contract prices for FY 2011; cost of monitoring and adverse events were taken from literature relating to direct comparison of warfarin and other novel oral anticoagulants (namely dabigatran).

Because cost of drug can vary over time and estimates of INR monitoring cost vary widely, we performed a sensitivity analysis on these two variables to examine their effect on the final cost of therapy. When drug cost was adjusted, it was determined that rivaroxaban would have to cost $21.79/patient/month in order to provide equal value to warfarin (11% of its current cost), or $154.65/patient/month in order to provide equal value to dabigatran (79% of its current cost). For comparison, at VA contract prices, drug cost of warfarin is approximately $1.50/patient/month.

Similarly, INR monitoring would have to cost $1931/patient/year for equal cost-efficacy of rivaroxaban. Estimates of monitoring cost vary, but our base case assumed monitoring cost of $186/patient/year (less than 10% of this value).

In evaluation of a patient subgroup at higher risk for events/complications, rivaroxaban was similarly not found to provide equal value to warfarin. However, in evaluating data, we identified patient populations whose benefit from rivaroxaban or dabigatran may have been more difficult to quantify, including patients at high risk for complications from anticoagulant therapy, patients where adherence or consistent vitamin K intake is a concern, and patients where geographic access to laboratory/clinic is limited.

This analysis did not include possible evidence of an antidote for rivaroxaban, which may increase its therapeutic value in clinical practice.

**Executive Summary**

**Clinical Benefits**

Begin with the FDA approved indication of the drug and summarize the clinical benefits in terms of efficacy and effectiveness, safety and tolerability, and the current need for this therapy based on the shortcomings of the currently available treatment options.

**Economic Benefits**

Rivaroxaban is a novel oral anticoagulant and does not require regular monitoring of INR/other values for clinical efficacy. Additionally, there is some evidence of an antidote for rivaroxaban, providing for another possible scenario where this drug is preferred. It is currently the more expensive per unit than the two standards of care (dabigatran and warfarin), although this may change in the future.

**Budget Impact Analysis**

Treating VA patients with atrial fibrillation with rivaroxaban would cost the VA an additional $162.9 million per year compared to warfarin, or $41.3 million per year compared to dabigatran. At this time, we found no patient subgroup where rivaroxaban is the preferred therapy; however, patients with compliance issues or difficulty obtaining regular INR tests may benefit from rivaroxaban therapy.

Conclusion

At this time, rivaroxaban does not provide equal value to other standards of care in treating atrial fibrillation. Despite lack of necessary monitoring, significantly higher cost of drug precludes regular use at this time. If the cost of rivaroxaban decreases in the future, it may provide equal value to dabigatran (one standard of care) in this population; however, it cannot be recommended for widespread use currently.

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