CLINICAL UPDATE

Brand Name	Xarelto®
Generic Name	rivaroxaban
Drug Manufacturer	Janssen Pharmaceuticals, Inc.

Clinical Update

TYPE OF CLINICAL UPDATE

Clinical Update - New Dosage Form

FDA APPROVAL DATE

December 12, 2021

LAUNCH DATE

January 6, 2022

REVIEW DESIGNATION

Priority

TYPE OF REVIEW

Type 3 - New Dosage Form

DISPENSING RESTRICTIONS

N/A

Overview

INDICATION(S) FOR USE

Xarelto® is a factor Xa inhibitor indicated:

- to reduce risk of stroke and systemic embolism in nonvalvular atrial fibrillation.
- for treatment of deep vein thrombosis (DVT).
- for treatment of pulmonary embolism (PE).
- for reduction in the risk of recurrence of DVT or PE.
- for the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery.
- for prophylaxis of venous thromboembolism (VTE) in acutely ill medical patients.
- to reduce the risk of major cardiovascular events in patients with coronary artery disease (CAD).
- to reduce the risk of major thrombotic vascular events in patients with peripheral artery disease (PAD), including patients after recent lower extremity revascularization due to symptomatic PAD.
- for treatment of VTE and reduction in the risk of recurrent VTE in pediatric patients from birth to less than 18 years.
- for thromboprophylaxis in pediatric patients 2 years and older with congenital heart disease after the Fontan procedure.

MECHANISMS OF ACTION

Xarelto® is a selective inhibitor of FXa. It does not require a cofactor (such as Anti-thrombin III) for activity. Rivaroxaban inhibits free FXa and prothrombinase activity. Rivaroxaban has no direct effect on platelet

aggregation, but indirectly inhibits platelet aggregation induced by thrombin. By inhibiting FXa, rivaroxaban decreases thrombin generation.

DOSAGE FORM(S) AND STRENGTH(S)

Tablets: 2.5 mg, 10 mg, 15 mg, and 20 mg.
For oral suspension: 1 mg/mL once reconstituted.

DOSE & ADMINISTRATION

- Nonvalvular Atrial Fibrillation: 15 or 20 mg, once daily with food
- Treatment of DVT and/or PE: 15 mg orally twice daily with food for the first 21 days followed by 20 mg orally once daily with food for the remaining treatment.
- Reduction in the Risk of Recurrence of DVT and/or PE in patients at continued risk for DVT and/or PE: 10 mg once daily with or without food, after at least 6 months of standard anticoagulant treatment.
- Prophylaxis of DVT Following Hip or Knee Replacement Surgery: 10 mg orally once daily with or without food.
- Prophylaxis of VTE in Acutely Ill Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding: 10 mg once daily, with or without food, in hospital and after hospital discharge for a total recommended duration of 31 to 39 days.
- CAD or PAD: 2.5 mg orally twice daily with or without food, in combination with aspirin (75-100 mg) once daily.

EFFICACY

1. Stroke Prevention in Nonvalvular Atrial Fibrillation

A multi-national, double-blind study comparing Xarelto® (at a dose of 20 mg once daily with the evening meal in patients with CrCl >50 mL/min and 15 mg once daily with the evening meal in patients with CrCl 30 to 50 mL/min) to warfarin (titrated to INR 2.0 to 3.0) to reduce the risk of stroke and non-central nervous system (CNS) systemic embolism in patients with nonvalvular atrial fibrillation (AF). Patients had to have one or more of the following additional risk factors for stroke:

- A prior stroke (ischemic or unknown type), transient ischemic attack (TIA) or non-CNS systemic embolism, or.
- 2 or more of the following risk factors: o age ≥75 years, o hypertension, o heart failure or left ventricular ejection fraction ≤35%, or o diabetes mellitus.

Table: Primary Composite Endpoint Results in ROCKET AF Study (Intent-to-Treat Population)

	XARELTO		Warfarin		XARELTO vs. Warfarin
Event	N=7081 n (%)	Event Rate (per 100 Pt-yrs)	N=7090 n (%)	Event Rate (per 100 Pt-yrs)	Hazard Ratio (95% CI)
Primary Composite Endpoint*	269 (3.8)	2.1	306 (4.3)	2.4	0.88 (0.74, 1.03)
Stroke	253 (3.6)	2.0	281 (4.0)	2.2	
Hemorrhagic Stroke†	33 (0.5)	0.3	57 (0.8)	0.4	
Ischemic Stroke	206 (2.9)	1.6	208 (2.9)	1.6	
Unknown Stroke Type	19 (0.3)	0.2	18 (0.3)	0.1	
Non-CNS Systemic Embolism	20 (0.3)	0.2	27 (0.4)	0.2	

* The primary endpoint was the time to first occurrence of stroke (any type) or non-CNS systemic embolism. Data are shown for all randomized patients followed to site notification that the study would end.

† Defined as primary hemorrhagic strokes confirmed by adjudication in all randomized patients followed up to site notification

2. **Reduction in the Risk of Recurrence of DVT and/or PE**:
EINSTEIN CHOICE Study Xarelto® for reduction in the risk of recurrence of DVT and of PE was evaluated in the EINSTEIN CHOICE study [NCT02064439], a multi-national, double-blind, superiority study comparing Xarelto® (10 or 20 mg once daily with food) to 100 mg acetylsalicylic acid (aspirin) once daily in patients who had completed 6 to 12 months of anticoagulant treatment for DVT and/or PE following the acute event. The intended treatment duration in the study was up to 12 months. Patients with an indication for continued therapeutic-dose anticoagulation were excluded.
In the EINSTEIN CHOICE study, Xarelto® 10 mg was demonstrated to be superior to aspirin 100 mg for the primary composite endpoint of time to first occurrence of recurrent DVT or nonfatal or fatal PE.

Table: Primary Composite Endpoint and its Components Results* in EINSTEIN CHOICE Study – Full Analysis Set

Event	XARELTO 10 mg N=1,127 n (%)	Acetylsalicylic Acid (Aspirin) 100 mg N=1,131 n (%)	XARELTO 10 mg vs. Aspirin 100 mg Hazard Ratio (95% CI)
Primary Composite Endpoint	13 (1.2)	50 (4.4)	0.26 (0.14, 0.47) p<0.0001
Symptomatic recurrent DVT	8 (0.7)	29 (2.6)	
Symptomatic recurrent PE	5 (0.4)	19 (1.7)	
Death (PE)	0	1 (<0.1)	
Death (PE cannot be excluded)	0	1 (<0.1)	

* For the primary efficacy analysis, all confirmed events were considered from randomization up to the end of intended treatment duration (12 months) irrespective of the actual treatment duration. The individual component of the primary endpoint represents the first occurrence of the event.

3. **Prophylaxis of Deep Vein Thrombosis Following Hip or Knee Replacement Surgery**
Xarelto® was studied in 9011 patients (4487 Xarelto® -treated, 4524 enoxaparin-treated patients) in the Regulation of Coagulation in Orthopedic Surgery to Prevent DVT and PE, Controlled, Double-blind, Randomized Study of BAY 59-7939 in the Extended Prevention of VTE in Patients Undergoing Elective Total Hip or Knee Replacement (RECORD 1, 2, and 3) [NCT00329628, NCT00332020, NCT00361894] studies.
One randomized, double-blind, clinical study (RECORD 3) in patients undergoing elective total knee replacement surgery compared Xarelto® 10 mg once daily started at least 6 to 8 hours (about 90% of patients dosed 6 to 10 hours) after wound closure versus enoxaparin. In RECORD 3, the enoxaparin regimen was 40 mg once daily started 12 hours preoperatively. The mean age (± SD) of patients in the study was 68 ± 9.0 (range 28 to 91) years with 66% of patients ≥65 years. Sixty-eight percent (68%) of patients were female. Eighty-one percent (81%) of patients were White, less than 7% were Asian, and less than 2% were Black. The study excluded patients with severe renal impairment defined as an estimated creatinine clearance.

Table: Summary of Key Efficacy Analysis Results for Patients Undergoing Total Knee Replacement Surgery - Modified Intent-to-Treat Population

	RECORD 3		
Treatment Dosage and Duration	**XARELTO 10 mg once daily**	**Enoxaparin 40 mg once daily**	**RRR*, p-value**
Number of Patients	**N=813**	**N=871**	
Total VTE	79 (9.7%)	164 (18.8%)	48% (95% CI: 34, 60), p<0.001
Components of events contributing to Total VTE			
Proximal DVT	9 (1.1%)	19 (2.2%)	
Distal DVT	74 (9.1%)	154 (17.7%)	
Non-fatal PE	0	4 (0.5%)	
Death (any cause)	0	2 (0.2%)	
Number of Patients	**N=895**	**N=917**	
Major VTE†	9 (1.0%)	23 (2.5%)	60% (95% CI: 14, 81), p = 0.024
Number of Patients	**N=1206**	**N=1226**	
Symptomatic VTE	8 (0.7%)	24 (2.0%)	

* Relative Risk Reduction; CI = confidence interval

† Proximal DVT, nonfatal PE or VTE-related death

4. **Prophylaxis of Venous Thromboembolism in Acutely Ill Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding,**

The efficacy and safety of Xarelto® for prophylaxis of venous thromboembolism in acutely ill medical patients at risk for thromboembolic complications not at high risk of bleeding was evaluated in the MAGELLAN study (Multicenter, randomized, parallel Group Efficacy and safety study for the prevention of venous thromboembolism in hospitalized medically ill patients comparing rivaroxaban with enoxaparin [NCT00571649]). MAGELLAN was a multicentre, randomized, double-blind, parallel-group efficacy and safety study comparing Xarelto® to enoxaparin, in the prevention of VTE in hospitalized acutely ill medical patients during the in-hospital and post-hospital discharge period. Eligible patients included adults who were at least 40 years of age, hospitalized for an acute medical illness, at risk of VTE due to moderate or severe immobility, and had additional risk factors for VTE. The population at risk of VTE was required to have one or more of the following VTE risk factors, i.e., prolonged immobilization, age ≥75 years, history of cancer, history of VTE, history of heart failure, thrombophilia, acute infectious disease contributing to the hospitalization and BMI ≥35 kg/m2).

Table: Efficacy Results at Day 35 (modified Intent-to-Treat) and at Day 10 (per protocol) in the MAGELLAN Study

Events from Day 1 to Day 35, mITT analysis set	**XARELTO 10 mg N=2967 n (%)**	**Enoxaparin 40 mg/ placebo N=3057 n (%)**	**RR (95% CI)**
Primary Composite Endpoint at Day 35	131 (4.4%)	175 (5.7%)	0.77 (0.62, 0.96)
Symptomatic non-fatal PE	10 (0.3)	14 (0.5)	
Symptomatic DVT in lower extremity	13 (0.4)	15 (0.5)	
Asymptomatic proximal DVT in lower extremity	103 (3.5)	133 (4.4)	
VTE related death	19 (0.6)	30 (1.0)	
Events from Day 1 to Day 10, PP analysis set	**XARELTO 10 mg N=2938 n (%)**	**Enoxaparin 40 mg N=2993 n (%)**	**RR (95% CI)**
Primary Composite Endpoint at Day 10	78 (2.7)	82 (2.7)	0.97 (0.71, 1.31)
Symptomatic non-fatal PE	6 (0.2)	2 (<0.1)	
Symptomatic DVT in lower extremity	7 (0.2)	6 (0.2)	
Asymptomatic proximal DVT in lower extremity	71 (2.4)	71 (2.4)	
VTE related death	3 (0.1)	6 (0.2)	
mITT analysis set plus all-cause mortality	**N=3096 n (%)**	**N=3169 n (%)**	**RR (95% CI)**
Other Composite Endpoint at Day 35	266 (8.6)	293 (9.2)	0.93 (0.80, 1.09)
Symptomatic non-fatal PE	10 (0.3)	14 (0.4)	
Symptomatic DVT in lower extremity	13 (0.4)	15 (0.5)	
Asymptomatic proximal DVT in lower extremity	103 (3.3)	133 (4.2)	
All-cause mortality	159 (5.1)	153 (4.8)	

mITT: modified intent-to-treat; PP: per protocol; DVT: Deep vein thrombosis; PE: pulmonary embolism; VTE: venous thromboembolism; CI: Confidence Interval; RR: Relative Risk

5. Reduction of Risk of Major Cardiovascular Events in Patients with CAD

The evidence for the efficacy and safety of Xarelto® for the reduction in the risk of stroke, myocardial infarction, or cardiovascular death in patients with coronary artery disease (CAD) or peripheral artery disease (PAD) was derived from the double-blind, placebo-controlled Cardiovascular Outcomes for People using Anticoagulation Strategies trial (COMPASS) [NCT10776424]. A total of 27,395 patients were evenly randomized to rivaroxaban 2.5 mg orally twice daily plus aspirin 100 mg once daily, rivaroxaban 5 mg orally twice daily alone, or aspirin 100 mg once daily alone. Patients with established CAD or PAD were eligible. Patients with CAD who were younger than 65 years of age were also required to have documentation of atherosclerosis involving at least two vascular beds or to have at least two additional cardiovascular risk factors (current smoking, diabetes mellitus, an estimated glomerular filtration rate [eGFR]< 60 mL per minute, heart failure, or non-lacunar ischemic stroke ≥1 month earlier). Patients with PAD were either symptomatic with ankle brachial index < 0.90 or had asymptomatic carotid artery stenosis ≥50%, a previous carotid revascularization procedure, or established ischemic disease of one or both lower extremities. Patients were excluded for use of dual antiplatelet, other non-aspirin antiplatelet, or oral anticoagulant therapies, ischemic, non-lacunar stroke within 1 month, hemorrhagic or lacunar stroke at any time, or eGFR <15 mL/min.

Table-Efficacy results from COMPASS CAD Population

Event	XARELTO† N=8313		Placebo† N=8261		Hazard Ratio (95% CI)‡
	n (%)	Event Rate (%/year)	n (%)	Event Rate (%/year)	
Stroke, MI or CV death	347 (4.2)	2.2	460 (5.6)	2.9	0.74 (0.65, 0.86)
- Stroke	74 (0.9)	0.5	130 (1.6)	0.8	0.56 (0.42, 0.75)
- MI	169 (2.0)	1.1	195 (2.4)	1.2	0.86 (0.70, 1.05)
- CV death	139 (1.7)	0.9	184 (2.2)	1.1	0.75 (0.60, 0.93)
Coronary heart disease death, MI, ischemic stroke, acute limb ischemia	299 (3.6)	1.9	411 (5.0)	2.6	0.72 (0.62, 0.83)
- Coronary heart disease death§	80 (1.0)	0.5	107 (1.3)	0.7	0.74 (0.55, 0.99)
- Ischemic stroke	56 (0.7)	0.3	114 (1.4)	0.7	0.49 (0.35, 0.67)
- Acute limb ischemia#	13 (0.2)	0.1	27 (0.3)	0.2	0.48 (0.25, 0.93)
CV death,¶ MI, ischemic stroke, acute limb ischemia	349 (4.2)	2.2	470 (5.7)	3.0	0.73 (0.64, 0.84)
All-cause mortality	262 (3.2)	1.6	339 (4.1)	2.1	0.77 (0.65, 0.90)

* intention to treat analysis set, primary analyses.
† Treatment schedule: XARELTO 2.5 mg twice daily vs placebo. All patients received aspirin 100 mg once daily as background therapy.
‡ XARELTO vs. placebo.
§ Coronary heart disease death: death due to acute MI, sudden cardiac death, or CV procedure.
¶ CV death includes CHD death, or death due to other CV causes or unknown death.
# Acute limb ischemia is defined as limb-threatening ischemia leading to an acute vascular intervention (i.e., pharmacologic, peripheral arterial surgery/reconstruction, peripheral angioplasty/stent, or amputation).
CHD: coronary heart disease, CI: confidence interval; CV: cardiovascular; MI: myocardial infarction