XARELTO® (rivaroxaban) – Medicaid Testimony – P&T Committee Meeting

Submitted to Montana Medicaid by Janssen Scientific Affairs, LLC

CURRENT INDICATIONS

Xarelto® (rivaroxaban) is indicated for treatment of deep vein thrombosis (DVT), treatment of pulmonary embolism (PE), for the reduction in the risk of recurrence of DVT and/or PE in patients at continued risk for recurrent DVT and/or PE after completion of initial treatment lasting at least 6 months, to reduce the risk of stroke and systemic embolism (SE) in patients with nonvalvular atrial fibrillation (NVAF), prophylaxis of DVT, which may lead to PE in patients undergoing hip or knee replacement surgery, for the prophylaxis of venous thromboembolism (VTE) and VTE related death during hospitalization and post hospital discharge in adult patients admitted for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE and not at high risk of bleeding, and in combination with aspirin, to reduce the risk of major cardiovascular events (cardiovascular (CV) death, myocardial infarction (MI) and stroke) in patients with chronic coronary artery disease (CAD) or peripheral artery disease (PAD).[1]

KEY PRESCRIBING INFORMATION (PI) UPDATES[1]

The XARELTO® Prescribing Information has been updated. The revision date is November 2019. Recent key updates include the following[1]:

- **A new medically ill indication based on MAGELLAN study**: XARELTO is indicated for the prophylaxis of venous thromboembolism (VTE) and VTE related death during hospitalization and post hospital discharge in adult patients admitted for an acute medical illness who are at risk for thromboembolic complications due to moderate or severe restricted mobility and other risk factors for VTE and not at high risk of bleeding.[1]
  - DOSAGE AND ADMINISTRATION updated to include dosage recommendations for the new medically ill indication: CrCl ≥30 mL/min: 10 mg once daily, in hospital and after hospital discharge, for a total recommended duration of 31 to 39 days, take with or without food; CrCl<30 mL/min: Avoid use
- Sections titled DOSAGE AND ADMINISTRATION, WARNINGS AND PRECAUTIONS and USE IN SPECIFIC POPULAIONS including renal considerations for the following indications below have been updated. The creatinine clearance (CrCl) ranges and applicable footnotes for these indications have been updated from CrCl <30 mL/min to CrCl <15 mL/min in Table 1 titled: Recommended Dosage, specifically renal considerations column.
  - Treatment of DVT and/or PE, Reduction in the Risk of Reccurrence of DVT and/or PE in patients at continued risk for DVT and/or PE, Prophylaxis of DVT following: Hip Replacement Surgery; Knee Replacement Surgery, Prophylaxis of VTE in Acutely Ill Medical Patients at Risk for Thromboembolic Complications Not at High Risk of Bleeding

****See full PI for dosing and complete efficacy and safety information***

CLINICAL STUDY

MAGELLAN Subpopulation

Spyropoulos et al (2019)[2] conducted a retrospective, benefit-risk analysis in a subpopulation of the MAGELLAN study.

- Five risk factors for major bleeding were identified and applied as exclusion criteria to the MAGELLAN study to identify a subpopulation (~80% of the overall population) with potentially improved benefit-risk balance. The exclusion criteria were: history of bronchiectasis, pulmonary cavitation, or pulmonary hemorrhage, active cancer (i.e. undergoing acute, in-hospital treatment), active gastroduodenal ulcer in the three months prior to treatment, history of bleeding in the three months prior to treatment, or dual antiplatelet therapy.
- Except for history of cancer, baseline characteristics in the subpopulation were similar to those observed in the original population and were similar between treatment groups.
- The efficacy observed in the overall MAGELLAN population was maintained in the MAGELLAN subpopulation. In the MAGELLAN subpopulation, rates of any VTE event were consistent with the MAGELLAN overall population at day 10 and day 35. Major bleeding rates were similar in the rivaroxaban arm and the enoxaparin/placebo arm in the MAGELLAN subpopulation.

Retrospective Analysis of the MAGELLAN and MARINER Studies:

Weitz et al (2020)[3] conducted a retrospective analysis of the MAGELLAN and MARINER studies to identify the optimal dose of rivaroxaban for thromboprophylaxis in acutely ill medical patients with impaired renal function. The analysis also included the MAGELLAN subpopulation described previously.

- The relative risk of symptomatic VTE and VTE-related mortality at day 35 in the MAGELLAN subpopulation was similar among patients with and without renal impairment receiving rivaroxaban 10 mg. The hazard ratio of this parameter in the MARINER study was higher among patients with renal impairment receiving rivaroxaban 7.5 mg than those without renal impairment receiving rivaroxaban 10 mg. See Table: Outcomes at Day 35 in the MAGELLAN Subpopulation and MARINER Study.

Outcomes at Day 35 in the MAGELLAN Subpopulation and MARINER Study[3]

RR/HR (95% CI)[a]	MAGELLAN Subpopulation		MARINER	
	CrCl 30-<50	CrCl ≥50	CrCl 30-<50	CrCl ≥50
Total VTE and VTE-related death	0.66 (0.41-1.05)	0.70 (0.51-0.97)	-	-
Symptomatic VTE and VTE-related death	0.62 (0.27-1.44)	0.78 (0.44-1.40)	1.00 (0.52-1.92)	0.67 (0.43-1.04)
Major bleeding	2.09 (0.51-8.53)	1.28 (0.60-2.73)	NAb	1.44 (0.62-3.37)

Clinically relevant bleeding[c]	2.25 (1.20-4.22)	2.29 (1.54-3.21)	1.59 (0.72-3.50)	1.72 (1.21-2.43)

Abbreviations: CI, confidence interval; CrCl, creatinine clearance; HR, hazard ratio; NA, not applicable; RR, relative risk; VTE, venous thromboembolism. aRivaroxaban vs enoxaparin/placebo. RR for the MAGELLAN subpopulation and HR for the MARINER study. bThe incidence was 0.37% with rivaroxaban 7.5 mg vs 0% with placebo. cClinically relevant bleeding was defined as the composite of major and clinically relevant nonmajor bleeding.

- Rivaroxaban exposure in terms of area under the concentration-time curve at steady state (AUC_{ss}) was 12.2% higher with the 10 mg dose in patients with vs without renal impairment in the MAGELLAN study. Rivaroxaban exposure was 9.4% lower with the 7.5 mg dose in patients with renal impairment vs the 10 mg dose in those without renal impairment in the MARINER study.

REAL WORLD EVIDENCE

Alberts et al (2020)[4] conducted a retrospective cohort study which compared rivaroxaban and warfarin for stroke and all-cause mortality risk reduction. Optum® Clinformatics database from July 2011 to December 2017 was used to identify patients who started treatment with rivaroxaban or warfarin within 30 days following initial diagnosis of nonvalvular atrial fibrillation (NVAF). Before NVAF diagnosis, patients had 6 months of continuous health plan enrollment and CHA_2DS_2-VASc score ≥2. Stroke severity was determined by the National Institutes of Health Stroke Scale (NIHSS), imputed based on machine learning algorithms.

- Stroke and all-cause mortality risks were compared by treatment using Cox proportional hazard regression, with inverse probability of treatment weighting (IPTW) to balance cohorts for baseline risk factors.
- During a mean follow-up of 27 months, 175 rivaroxaban treated and 536 warfarin treated patients developed a stroke.
- Rivaroxaban reduced stroke risk by 19% (hazard ratio [HR] 0.81, 95% CI 0.73–0.91) compared to warfarin.
- Analysis by stroke severity showed significant risk reductions with rivaroxaban of 48% for severe stroke (NIHSS score, 16–42; HR 0.52, 95% CI 0.33–0.82) and 19% for minor stroke (NIHSS score, 1 to <5; HR 0.81, 95% CI, 0.68–0.96).
- No significant difference was found for moderate stroke (NIHSS score, 5 to <16; HR 0.93, 95% CI, 0.78–1.10).
- A total of 41 rivaroxaban treated patients and 147 warfarin treated patients died poststroke, of which 12 and 67 died within 30 days, representing a 24% mortality risk reduction with rivaroxaban (HR 0.76, 95% CI, 0.61–0.95) poststroke and 59% reduction (HR 0.41, 95% CI, 0.28–0.60) within 30 days.

Barco et al (2020)[5] conducted The Home Treatment of Patients with Low-Risk Pulmonary Embolism with the Oral Factor Xa Inhibitor Rivaroxaban (HoT-PE) trial was a prospective, multicenter, single-arm investigator-initiated, phase 4 interventional trial which evaluated the efficacy and safety of rivaroxaban in early transition from hospital to ambulatory treatment in patients with low-risk acute PE. Patients were enrolled between May 2014 through June 2018.

Patients were treated with rivaroxaban 15 mg twice daily for the first three weeks followed by rivaroxaban 20 mg once daily for at least three months. Reduction of the maintenance dose to 15 mg once daily was possible at the discretion of the treating physician for patients with creatinine clearance below 50 mL/min, if the individual risk for bleeding was deemed to outweigh the risk for recurrent VTE. Patients were required to be discharged from the hospital within 48 hours of initial presentation for PE. [5] Eligibility criteria included absence of (i) haemodynamic instability, (ii) right ventricular dysfunction or intracardiac thrombi, and (iii) serious comorbidities. The majority of exclusion criteria was adapted from the Hestia management study, which includes excluding patients with active bleeding or known significant bleeding risk. Additional exclusion criteria included: need for supplemental oxygen administration; chronic treatment with anticoagulant drugs; pain requiring parenteral administration of analgesic agents; other medical conditions requiring hospitalization; non-compliance or inability to adhere to the treatment or the follow-up visits, or lack of a family environment or support system; and contraindications to rivaroxaban as defined in the summary of product characteristics of the drug.[5]

- The primary efficacy endpoint was symptomatic recurrent VTE, or PE related death within 3 months of enrollment. Recurrent PE was defined as at least one of the following: (i) a new intraluminal filling defect on CTPA or pulmonary angiography; (ii) a new perfusion defect involving at least 75% of a segment with normal ventilation on lung scan; (iii) a nondiagnostic lung scan accompanied by evidence of (new) deep vein thrombosis on ultrasonography; new PE (fresh thrombi) at autopsy. [5]
- The safety endpoint included major bleeding (defined by the criteria of the International Society on Thrombosis and Haemostasis), clinically relevant non-major bleeding, and serious adverse events. [5]
- An interim analysis was planned after enrolment and 3-month evaluation of the first 525 patients in the ITT population, with the objective of early termination of the study if H_0 could be rejected at the level of a = 0.004; this corresponded to less than six symptomatic or fatal recurrent VTE events. Of 525 patients included in the interim analysis of the ITT population, 240 (45.7%) were women and the mean age was 57 years. [5]
- The primary endpoint analyses were performed in the ITT population, which included all patients who signed the informed consent. Safety analysis was conducted in the safety population, including all patients who received at least one dose of study drug.[5]
- The primary efficacy endpoint of symptomatic recurrent non-fatal VTE or PE related death within three months occurred in three [0.6%; one sided upper 99.6% confidence interval (CI) 2.1%; one-sided P-value <0.0001]. [5]
- Major bleeding occurred in 6 (1.2%; 95% confidence interval [CI]: 0.4–2.5) of the 519 patients, clinically relevant non-major bleeding occurred in 31 (6.0%; 95% CI: 4.1– 8.4) of 519 patients and serious adverse events occurred in 58 (11.2%; 95% CI 8.6–14.2) patients included in the safety population. [5]

REFERENCES

1.XARELTO (rivaroxaban) [Package insert]. Titusville, NJ: Janssen Pharmaceuticals, Inc; https://imedicalknowledge.veevavault.com/ui/approved_viewer?token=7994-2a7e16dc-2859-4486-a5a4-8838e35d61a6. **2.**Spyropoulos AC, Lipardi C, Xu J, et al. Improved benefit risk profile of rivaroxaban in a subpopulation of the MAGELLAN study. [published online ahead of print November 20, 2019]. *CATH*. doi:10.1177/1076029619886022.**3.** Weitz JI, Raskob GE, Spyropoulos AC, et al. Thromboprophylaxis with rivaroxaban in acutely ill medical patients with renal impairment: insights from the MAGELLAN and MARINER trials. [published online ahead of print January 23, 2020]. *Thromb Haemost*. doi:10.1055/s-0039-1701009. **4.** Alberts M, Chen YW, Lin JH, et al. Risks of stroke and mortality in atrial fibrillation patients treated with rivaroxaban and warfarin. *Stroke*. 2020;51:549-555. DOI: 510.1161/STROKEAHA.1119.025554. **5**. Barco S, Schmidtmann I, Ageno W, et al. Early discharge and home treatment of patients with low-risk pulmonary embolism with the oral factor Xa inhibitor rivaroxaban: an international multicentre single-arm clinical trial. *Eur Heart J*. 2020;41(4):509-518. doi: 510.1093/eurheartj/ehz1367.