

Request for permission for pharmaceutical industry oral testimony at Idaho Medicaid's P&T Committee meeting on 5-20-2016.

Submission # 5

As of May 5, 2016, this submission has not been accepted for oral presentation at the meeting.

Gennrich, Jane - Medicaid

From: Trivedi, Sheela [JRDUS] <strived6@ITS.JNJ.com>
Sent: Friday, April 29, 2016 8:33 AM
To: Eide, Tamara J. - Medicaid
Cc: Litzenberger, Laura [OMJUS]; Danyluk, Alexander [OMJUS]
Subject: XARELTO - Submission for Idaho Medicaid - May 20, 2016
Attachments: Idaho Medicaid Cover Letter 2016.pdf; Idaho Medicare Submission 2016.pdf; Xarelto PI.pdf

Dear Dr. Eide,

We are requesting that the P&T Chairman or their designee permit the enclosed new scientific data on **XARELTO® (rivaroxaban)** be presented orally by Laura Litzenberger, Janssen Scientific Affairs Liaison at the May 20th, 2016 P&T Committee meeting.

Please find attached a cover letter and summary of the new scientific data, including the prescribing information.

Please let me know if you have any questions or need anything additional.

Kind Regards,

Sheela Trivedi, PharmD,CDE

Manager, Medical Information -- Cardiovascular

Medical Information & Services

Janssen Scientific Affairs, LLC

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Raritan, NJ 08869
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April 29, 2016

Idaho Medicaid
Pharmacy & Therapeutics Committee
Attention: Tami Eide, PharmD
3232 Elder Street
Boise, ID 83705

Dear Dr. Eide:

Thank you for your interest in XARELTO® (rivaroxaban), marketed by Janssen Pharmaceuticals, Inc. The enclosed information has been supplied to you in response to your unsolicited request and is not intended as an endorsement of any usage not contained in the prescribing information.

Response(s):

- XARELTO – Idaho Medicaid Summary - 2016

For complete information, please refer to the enclosed full XARELTO Prescribing Information, including the following sections: **BOXED WARNING(S), INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS.**

If you have any additional questions, please contact us:

- Phone: 1-800-JANSSEN (1-800-526-7736) Monday-Friday, 9:00a.m.-8:00p.m
- Web Site: www.janssenmedinfo.com

To report a possible adverse event or product quality complaint, please call the Customer Communications Center immediately, at 1-800-JANSSEN (1-800-526-7736).

Please contact Laura Litzenberger if you need additional information at (520)751-4100 or LLitzenb@its.jnj.com.

Sincerely,

Sheela Trivedi, PharmD, CDE
Manager, Medical Information
Medical Information and Services

Case # 00571266



XARELTO® (rivaroxaban) Tablets Idaho Medicaid Summary

The following information is provided because of your specific unsolicited request and is not intended as an endorsement of any usage not contained in the Prescribing Information. For complete information, please refer to the enclosed full Prescribing Information, including the following sections: **BOXED WARNING(S), INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, and ADVERSE REACTIONS.**

Attention Idaho Medicaid Reviewer:

Please find enclosed your XARELTO® Medicaid summary in advance of the Idaho Medicaid meeting on May 20th, 2016. This information is provided as a professional courtesy in response to a request forwarded to us by Laura Litzenberger, PharmD, Principal Liaison, Health Economics and Clinical Outcomes Research Field -Janssen Scientific Affairs, LLC - Johnson & Johnson.

XARELTO®

- NEW STUDIES:

- Real world safety and efficacy data in non-valvular AF patients is consistent with the results from Phase 3 randomized, controlled clinical trials.²⁻³
- The international XANTUS study reported an incidence of major bleeding of 2.1 per 100 patient years, and an incidence of stroke and systemic embolism of 0.8 per 100 patient years in patients with nonvalvular atrial fibrillation in routine clinical practice.⁴
- A real world study which investigated the safety and efficacy of rivaroxaban compared to standard of care in patients with deep vein thrombosis found major bleeding occurred in 0.7% (19/2619) of patients compared with 2.3% (48/2149) of standard of care patients.⁵
- As part of the global CALLISTO oncology program³, an analysis was conducted based on clinical pathway guidelines to validate the safety and efficacy of rivaroxaban for use in cancer patients.⁶

- NEW PRODUCT INFORMATION:

- Updated product information from XARELTO® Full Prescribing Information¹

Please refer to the enclosed XARELTO® Full Prescribing Information for complete prescribing information.

XARELTO® (rivaroxaban) Tablets
Idaho Medicaid Summary

CLINICAL STUDIES:

Major Bleeding in a Post-Marketing Assessment of 39,052 Nonvalvular Atrial Fibrillation Patients on Rivaroxaban²

- An ongoing 5-year post-marketing safety surveillance study to gather safety data of rivaroxaban in patients with non-valvular atrial fibrillation (NVAF). Data from the first 2 years has been presented.
- Of the 39,052 NVAF patients on rivaroxaban, 970 experienced at least one major bleeding (MB) events, representing an incidence of 2.89 per 100 person-years. The most common site of bleeding was GI (87.2%), followed by intracranial (8.1%).
- A total of 35 patients in the MB group died during hospitalization, for a fatal bleeding rate of 0.10 per 100 person years (95% CI 0.07–0.15). Of the 35 patients who died, 26 (74.3%) had an intracranial hemorrhage, and 9 (25.7%) had GI bleeding.² The mean age at death was 80.3 years.³
- MB events were more prevalent in older patients, those with hypertension, coronary heart disease, heart failure, and renal disease, along with greater CHA2DS2-VASc scores.

XANTUS: a real-world prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation.⁴

- A prospective, observational, post-authorization, non-interventional, single-arm cohort study designed to assess the safety and efficacy of rivaroxaban for stroke prevention in NVAF in routine clinical practice.
- 10,934 patients from 311 sites were screened. The type, duration, dose of drug was determined by the treating physician. Data was collected at the start of therapy, hospital discharge, and every 3 months after for 1 year.
- The primary outcome was to assess the safety of rivaroxaban in routine practice, recorded as adverse events or serious AE, including MB (as defined by the ISTH criteria), all-cause death, and any other adverse events.
- Of the 6,784 patients included in the safety population, 5336 (78.7%) patients received rivaroxaban 20 mg once daily, 1410 (20.8%) received rivaroxaban 15 mg once daily, and 35 (0.5%) patients received a rivaroxaban dose besides the 15 or 20 mg once daily dose. The mean observation period was 329 days.
- The rate of MB (2.1 events per 100 person-years), thromboembolic events (1.8 events per 100 person-years) and all-cause death (1.9 events per 100 person-years) were low and increased over time. The incidence of MB events and symptomatic thromboembolic events was found to increase with age.
- All-cause death occurred in 118 patients with the adjudicated cause of death due primarily to cardiovascular causes (41.5%), followed by cancer (19.5%).
- 6522 patients (96.1%) did not experience any outcomes of treatment-emergent MB, all-cause death, or stroke/systemic embolism. MB was mostly treated using conservative methods while non-specific reversal agents were rarely used.
- Treatment persistence remained high over the 1-year period, with a discontinuation rate of 20.1%.

Safety and effectiveness of oral rivaroxaban versus standard anticoagulation for the treatment of symptomatic DVT⁵

- XALIA was a multicenter, prospective, non-interventional, international study designed to investigate the safety and efficacy of rivaroxaban compared with standard of care (SOC), which included unfractionated heparin, LMWH, or fondaparinux, usually overlapping and followed by VKA, in patients with DVT.
- Propensity score-adjusted analyses were included for 2505 rivaroxaban-treated patients and 2010 SOC-treated patients. The incidence of recurrent VTE in the rivaroxaban group compared with the SOC group was 1.4% (36/2505) versus 2.3% (47/2010), respectively; propensity-score adjusted HR 0.91 [95% CI 0.54-1.54], p=0.72).
- The incidence of all-cause mortality in the rivaroxaban group compared with the SOC group was 0.4% (11/2505) versus 3.4% (69/2010), respectively; propensity-score adjusted HR 0.51 [95% CI 0.24-1.07], p=0.074).
- Rates of major adverse cardiovascular events and other thromboembolic events were similar between treatment groups. Major bleeding was reported in 0.8% (19/2505) of patients in the rivaroxaban group and 2.1% (43/2010) of patients in the SOC group (HR 0.77; 95% CI 0.40-1.50; p=0.44) in the propensity score-adjusted analysis.

Safe and effective use of rivaroxaban for treatment of cancer-associated venous thromboembolic disease⁶

- As part of the global oncology program that included 9 studies with rivaroxaban (CALLISTO)⁷, an analysis was conducted based on clinical pathway guidelines to validate the safety and efficacy of rivaroxaban for use in cancer patients.
- Patients received a full course of anticoagulation with rivaroxaban and up to 3 days of parenteral anticoagulation. There were 200 patients with 6 months of follow-up who were included in the analysis (136 patients had PE with or without DVT and 64 patients had proximal, symptomatic lower extremity DVT).
- Solid tumors were reported in 183 patients and hematologic malignancies were reported in 17 patients. Of the patients with solid tumors (excluding brain tumors), 142 had stage 4 disease.
- Recurrent VTE and major bleeding occurred at an incidence of 4.4% (95% CI= 1.4%-7.4%) and 1.6% (95% CI= 0%-3.3%), respectively. The incidence of clinically relevant nonmajor bleeding leading to discontinuation of rivaroxaban was 3.8% (95% CI= 1.0%-6.6%).
- All-cause mortality occurred at an incidence of 18.2% (95% CI=12.2%-23.7%). There were no deaths related to bleeding.

NEW PRODUCT INFORMATION¹:

The following sections were updated from March 2015 – March 2016:

- **Clinical Trials Experience – Non-Valvular Atrial fibrillation** The bleeding events were amended: addition of intracranial hemorrhage, removal of critical organ bleed, transfusion, and other

components of major bleed, addition of HR and Confidence Intervals. A forest plot was added (*Figure 1*) (Section 6.1)

- Updated to clarify drug interaction studies in patients with normal versus impaired renal function and to further define the pharmacokinetic classification of fluconazole. Fluconazole is listed as a moderate CYP3A4 inhibitor and not a combined PGP/CYP3A4 inhibitor. (Section 7.1)
- Impaired renal function was defined as a CrCl less than 80 mL/min (<80). More specific clarification of the medications that are listed here. (Section 7.4)
- The effect of certain drugs on the pharmacokinetics of a NOAC were depicted in a plot rather than describing the study data in paragraph form. *Figure 2* was added. The overall recommendations on drug interactions have not changed. There was a change in language to the Anticoagulants section (*Neither enoxaparin nor warfarin did not affected the pharmacokinetics of rivaroxaban*), and a change in language to NSAIDs/Aspirin section (*Neither naproxen nor aspirin affected the pharmacokinetics of rivaroxaban*) (Section 12.3)
- *Figure 4* was added; The forest plot was amended to include the same subgroups as the plot in Section 6.1. The Intent-to-Treat (ITT) population was used to generate this forest plot. (Section 14.1)

MONOGRAPH INFORMATION:

The following errors / omissions were identified in the Magellan Anticoagulants Therapeutics Class Review:

1. The pharmacokinetics table (page 9) lists the half-life of rivaroxaban as 5 to 13 hours.
 - a. The terminal half-life of rivaroxaban is 5 to 9 hours in healthy subjects aged 20 to 45 years; 11 to 13 hours in the elderly.
2. The pharmacokinetics table (page 9) incorrectly lists the excretion of rivaroxaban as 66% by urine.
 - a. Approximately one-third of the administered compound is not metabolized, and so it leaves the body unchanged (as active drug) in the urine by direct renal excretion.
 - b. The remaining two-thirds of the administered compound is excreted as inactive metabolites in urine and feces.
 - c. The renal clearance of rivaroxaban is approximately 36%
3. The review (page 17; paragraph 4) discusses the rivaroxaban post-marketing observational surveillance study which included 27,467 patients.
 - a. An update to this ongoing 5-year post-marketing study was presented in 2015 which now includes data in 39,052 patients. [see reference #2 below]
 - b. The rate of major bleeding was 2.89 per 100-person years.
 - c. The rate of death due to bleeding was 0.10 per 100-person years.
 - d. The most common site of bleeding was gastrointestinal (87.2%), followed by intracranial (8.1%).
4. The review (page 21; paragraph 4) lists that rivaroxaban should be used with caution in patients with moderate renal impairment (CrCl 30 mL/min to < 50 mL/min) for DVT prophylaxis or treatment.
 - a. Avoid the use of XARELTO in patients with CrCl <30 mL/min due to an expected increase in rivaroxaban exposure and pharmacodynamic effects in this patient population

- b. Observe closely and promptly evaluate any signs or symptoms of blood loss in patients with CrCl 30 to 50 mL/min.
5. The Oral Dosages table (page 24) should indicate the rivaroxaban dose as:
- a. For patients with nonvalvular atrial fibrillation: 20 mg once daily with the evening meal
 - i. For patients with CrCl 15-50 mL/min: 15 mg once daily with the evening meal
 - b. For the treatment of DVT/PE: 15 mg twice daily with food x 21 days; 20 mg once daily with food thereafter
 - c. To prevent recurrence of DVT/PE: 20 mg once daily with food

References:

1. XARELTO® (rivaroxaban) Tablets Full Prescribing Information. Janssen Pharmaceuticals, Inc; Titusville, NJ
2. Peacock WF, Patel M, Tamayo S, et al. Major Bleeding in a Post-Marketing Assessment of 39,052 Nonvalvular Atrial Fibrillation Patients on Rivaroxaban. Scientific poster presented at European Society of Cardiology (ESC) 2015 Congress, August 29 - September 2, 2015; London, UK.
3. Tamayo S, Patel M, Yuan Z, et al. Post-Marketing Pharmacovigilance Study for the Active Detection and Evaluation of Major Bleeding in 39,052 Rivaroxaban Users with Non-valvular Atrial Fibrillation. Scientific poster presented at American College of Cardiology (ACC) Scientific Sessions, March 14-16, 2015; San Diego, CA, USA.
4. Camm AJ, Amarencu P, Haas S, et al. XANTUS: a real-world prospective, observational study of patients treated with rivaroxaban for stroke prevention in atrial fibrillation. *European Heart Journal*. doi: 10.1093/eurheartj/ehv466.
5. Ageno W, Mantovani LG, Haas S, et al. Safety and effectiveness of oral rivaroxaban versus standard anticoagulation for the treatment of symptomatic deep-vein thrombosis (XALIA): an international, prospective, non-interventional study. *Lancet Hematol* 2015. Published online December 7, 2015. [http://dx.doi.org/10.1016/S2352-3026\(15\)00257-4](http://dx.doi.org/10.1016/S2352-3026(15)00257-4).
6. Mantha S, Laube E, Miao Y, et al. Safe and effective use of rivaroxaban for treatment of cancer-associated venous thromboembolic disease: a quality improvement initiative. Data presented at the 57th ASH Annual Meeting & Exposition, Dec 5-8, 2015, Orlando, FL.
7. Janssen Research & Development, LLC. New Clinical Research Program Initiated for the Prevention and Treatment of Life-Threatening Blood Clots in Patients with Cancer. Raritan, NJ. May 28, 2015. Available at: <http://www.jnj.com/news/all/New-Clinical-Research-Program-Initiated-for-the-Prevention-and-Treatment-of-Life-Threatening-Blood-Clots-in-Patients-with-Cancer>. (Accessed: May 28, 2015).