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APPLICATION NUMBER:

206316Orig1Orig2s000

**RISK ASSESSMENT and RISK MITIGATION
REVIEW(S)**

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) Review

Date: January 5, 2015

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Drug Name(s): SAVAYSA (edoxaban)

Therapeutic Class: Factor Xa Inhibitor

Dosage and Route: 15 mg, 30 mg and 60 mg oral tablets

Application Type/Number: NDA 206316

Submission Number: ORIG-1 Submission Seq. No. 0000 dated 1/8/2014

Applicant/Sponsor: Daiichi-Sankyo, Inc.

OSE RCM #: 2014-65

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EXECUTIVE SUMMARY

This Division of Risk Management (DRISK) review provides the final evaluation of whether a risk evaluation and mitigation strategy (REMS) is needed for Savaysa¹ (edoxaban), for the proposed indication of reduction of the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF).

The Sponsor, Daiichi-Sanyo Pharma Development, submitted NDA 206316 on January 8, 2014 for the proposed AF indication. The NDA submission also included a separate proposed indication for treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE)^{(b) (4)} under review by the Division of Hematology Products (DHP). These indications have been reviewed by, DRISK under separate cover.² The Sponsor did not include a proposed REMS for either indication in their original submissions.

As of the date of this review, final labeling is still being negotiated between DCRP and the Sponsor. Currently proposed labeling recommends Indications and Usage language for AF that includes recommendations for a limitation of use in patients with select creatinine clearance level. Language appears throughout product labeling that aligns with efficacy findings related renal function, as discussed below in Sections 3, 4 and 6, including the Boxed Warning, Warnings and Precautions, Dosing and Administration, and Clinical Studies sections of the label.

Based on the currently available data in the submission, DRISK concludes that no REMS is necessary for edoxaban for the AF indication.

1 INTRODUCTION

The purpose of this review is to document the Division of Risk Management's (DRISK) final evaluation of the need for a risk evaluation and mitigation strategy (REMS) for edoxaban, NDA 206316, for the proposed indication of reduction of the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF). The Sponsor did not include a proposed REMS for in their submission.

1.1 BACKGROUND

Edoxaban (NDA 206316) is an orally active, selective Factor Xa inhibitor that is being developed as an anticoagulant^{(b) (4)}. This review will evaluate the need for a REMS for the proposed indication of reduction in the risk of stroke and system embolism in patients with nonvalvular AF. A separate DRISK review was conducted to evaluate the need for a REMS for the following indications: treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE)^{(b) (4)}.

DRISK

¹ The proposed Proprietary Name SAVAYSA is currently under review by the Division of Medication Error Prevention and Analysis (DMEPA).

² Yancy, C. Risk Evaluation and Mitigation Strategy (REMS) Review for edoxaban (NDA 206316) [DVT and PE indication] dated September 17, 2014

³ Yancey, C. Division of Risk Management, Risk Evaluation and Mitigation Strategy (REMS) Review for Savaysa (edoxaban) dated September 17, 2014.

concluded that a REMS was not necessary to ensure the benefits outweighed the risks for the treatment of DVT and PE.

Subsequent to discussions between DCRP and the Sponsor, including a meeting of the Cardiovascular and Renal Drugs Advisory Committee (AC), the final agreed upon AF indication includes a 'Limitations of Use' in select patients based on creatinine clearance (CrCL) level, which draws upon DCRP's subgroup analysis showing a relationship between efficacy and renal function.⁴ Edoxaban labeling includes related language that aligns with these findings in the Boxed Warning, Indications and Usage, Dosage and Administration, Warnings and Precautions and Clinical Studies sections of labeling.

1.2 REGULATORY HISTORY

Please reference DRISK REMS Review dated October 8, 2014 (C. Miller) for additional regulatory history related to NDA 206316.

On January 8, 2014, the Agency received an original NDA from Daiichi-Sanyo for edoxaban for the proposed indications of reduction in the risk of stroke and system embolism in patients with nonvalvular AF. The Sponsor did not propose a REMS.

On June 12, 2014, the internal mid-cycle meeting was held for the edoxaban AF indication. Although efficacy results showed that edoxaban was non-inferior to warfarin in the pivotal ENGAGE-AF trial, there were select key efficacy issues identified.

- An interaction between efficacy results and renal function. A subgroup analysis showed that patients with renal impairments had better outcomes than patients with normal renal function, which called the appropriate dose into question.
- Additionally, efficacy findings showed that the Sponsor's dose adjustment (DA) strategy to decrease (by half) the edoxaban dose for subjects with renal insufficiency, low weight and concomitant P-gp inhibitors resulted in a decrease in efficacy in subjects who were dose reduced for low weight and concomitant P-gP inhibition; which called the DA strategy into question.

Key safety findings identified prior to the mid-cycle meeting included major bleeding, hepatic abnormalities, and worse net clinical benefit for edoxaban (compared to warfarin) among subjects with normal renal function.

On June 18, 2014, a teleconference was held between the edoxaban review team for the AF indication, led by DCRP, and the Sponsor, to provide formal notification of plans to convene a meeting of the Cardiovascular and Renal Drug Products Advisory Committee (AC) to discuss the AF indication portion of the edoxaban NDA. Also discussed with the Sponsor, in the context of the AC plans, were preliminary highlights of findings about the interaction between efficacy results and renal function. DCRP stated that discussions at the AC would likely include these key efficacy findings and the associated benefit-risk assessment of efficacy and safety for edoxaban. The AC was scheduled for October 30, 2014.⁵

⁴ Blank, M. (clinical efficacy) and McDowell, T. (clinical safety) Division of Cardiovascular and Renal Products Clinical Review of Safety and Efficacy for Edoxaban (NDA 206316) dated October 3, 2014.

⁵ [Federal Register Announcement](#) for the October 30, 2014 Cardiovascular and Renal Drugs Advisory Committee Meeting (posted September 17, 2014).

On June 24, 2014, the edoxaban mid-cycle communication meeting/teleconference was held with the Sponsor. All preliminary findings, as cited above, were reviewed with the Sponsor.

On August 6, 2014, DCRP held a face-to-face meeting with the Sponsor. The Sponsor provided preliminary modeling and other analyses (not formally submitted) relevant to discussions surrounding exposure matching for optimal edoxaban dosing as introduced by DCRP at the mid-cycle meeting teleconference.

On August 27, 2014, DCRP held a teleconference with the Sponsor to review issues surrounding the interaction between efficacy and renal function and additional data about exposure matching for optimal edoxaban dosing.

On September 29, 2014, DCRP sent the Sponsor the Late Cycle Meeting background package which included any substantive review issues, in preparation for the scheduled late cycle meeting. DRISK comments provided in the letter included the following:

- **Atrial Fibrillation (ORIG-1)** Edoxaban (NDA 206316) is currently under review for the proposed indication of the reduction in the risk of stroke and system embolism in patients with nonvalvular AF. The Division of Risk Management (DRISK) review team for this indication cannot make final determinations about the need for a Risk Evaluation and Mitigation Strategy (REMS) for edoxaban until the risk-benefit profile is further discussed at the October 30, 2014 meeting of the Cardiovascular and Renal Drugs Advisory Committee (AC). Following AC discussions, including the committee's recommendations about the safety and efficacy profile of edoxaban, DRISK will make a recommendation on risk management strategies for the product.
- **Treatment of deep vein thrombosis and pulmonary embolism (ORIG-2)** (b) (4)

(b) (4)
No issues that would require a REMS for the VTE indication have been identified to date.

On October 8, 2014, the edoxaban Late Cycle Meeting with the Sponsor was held as which time there was discussion from each reviewing discipline about current findings, to date.⁶

On October 30, 2014, the Cardiovascular and Renal Drugs AC meeting was held to discuss Edoxaban NDA 206316 for the proposed indication of reduction of the risk of stroke and systemic embolism in patients with nonvalvular AF. The meeting included discussion of the following overall findings supporting effectiveness: both edoxaban high exposure [E60/30] regimen and edoxaban low exposure [E30/15] were non-inferior to warfarin for the primary endpoint (see Section 3 below for detailed discussed on of findings).

On November 17, 2014, DCRP met with the Sponsor to review information discussed at the October 30, 2014 AC as well as next steps, with regard to issues surrounding dosing for the AF indication. Discussions included the consideration of (b) (4) a higher than studied dose to align with pharmacometric modeling showing increased efficacy with little change to the safety profile.

On November 18, 2014, DCRP met internally to further discuss labeling options for edoxaban, to include the proposal to approve the 60mg QD dose with a limitation of use (b) (4) along with related proposed labeling revisions to the Boxed Warning, Dosage and Administration, and Warnings and Precautions section of the label. The proposed label was subsequently emailed to the sponsor by DCRP.

⁶ Division of Cardiovascular and Renal Drugs (DCRP) October 8, 2014 Late Cycle Meeting Minutes for Edoxaban (NDA 206316) dated November 7, 2014.

On November 20, 2014, the Sponsor contacted DCRP by telephone, with a counter-proposal to the November 18, 2014 label proposed by DCR (b) (4)

On December 5, 2014, the sponsor submitted draft labeling via email to DCRP, which incorporated proposed dosing options and additional information related to renal function. Proposed dosing in Section 2 – Dosage and Administration for the AF indication included:

- CrCL 15 to 50 mL/min: 30 mg once daily
- CrCL >50 to < (b) (4) mL/min: 60 mg once daily

Proposed labeling also included language in Section 8 – Use in Specific Populations stating that (b) (4)

On December 12, 2014, DCRP met with senior leadership to discuss regulatory options for the AF indication. The application findings, specifically with regard to the proposal (b) (4)

On December 23, 2014, and January 5, 2015, a teleconference was held between DCRP and the sponsor to discuss labeling for edoxaban for the AF indication.

2 MATERIALS REVIEWED

2.1 SUBMISSIONS

- Daiichi-Sankyo Original NDA Submission (ORIG-1) for edoxaban (Seq. No. 0000) submitted January 8, 2014

2.2 OTHER MATERIALS INFORMING OUR REVIEW

- Blank, M., Lawrence, J., and McDowell, Z., DCRP Mid-Cycle presentation slides for edoxaban (Clinical, Statistics and Safety), held June 12, 2014 (internal) and June 24, 2014 (teleconference with Daiichi-Sankyo)
- Earp, J., Menon-Anderson, D and Madabushi, R. Office of Clinical Pharmacology Mid-Cycle presentation slides for edoxaban (Clinical Pharmacology and Pharmacometric) held June 12, 2014 (internal) and June 24, 2014 (teleconference with Daiichi-Sankyo)
- Stockbridge, N. DCRP Late Cycle Meeting Background Package for edoxaban dated September 29, 2014
- Blank, M. and McDowell, Z, Division of Cardiovascular and Renal Products, Clinical Review of Safety and Efficacy for edoxaban dated October 3, 2014
- DCRP Briefing Package and Slide Presentations from the October 30, 2014 meeting of the Cardiovascular and Renal Drug Product Advisory Committee.
- Daiichi-Sankyo Slide Presentations from the October 30, 2014 meeting of the Cardiovascular and Renal Drug Product Advisory Committee.

- Rose, M., Division of Cardiovascular and Renal Products, Cross-Discipline Team Leader Review Memorandum dated December 8, 2014.

3 SUMMARY OF THE EDOXABAN CLINICAL DEVELOPMENT PROGRAM⁷

Efficacy for edoxaban was evaluated for the AF indication in one Phase 3 pivotal registration study (DU176b C-U301), also known as ENGAGE AF-TIMI 48 (ENGAGE AF). ENGAGE AF was a double-blind, randomized, controlled study that included 21,105 subjects with AF treated for a median duration of 2.5 years and followed for a median duration of 2.8 years. The trial evaluated the efficacy and safety of the high and low dosing regimens of edoxaban (edoxaban 60 mg group and edoxaban 30 mg group) administered once daily in comparison to warfarin. In both edoxaban treatment groups, the dose was halved for subjects with moderate renal impairment ($\text{CrCL} \geq 30$ and ≤ 50 mL/min), low body weight (≤ 60 kg), or for subjects receiving concomitant P-glycoprotein (P-gp) inhibitors (verapamil, quinidine, dronedarone⁸), allowing for optimization of the dose at the start of treatment. Increases or decreases in edoxaban doses, including decrease from 60 mg to 30 mg (E60/30) and 30 mg to 15 mg (E30/15), as well as increases from 15 mg to 30 mg and 30 mg to 60 mg, were allowed throughout the study in response to a change in a subject's condition.

The primary efficacy objective of the study was to compare edoxaban to warfarin with regard to the time to first occurrence of a composite primary endpoint of stroke and systemic embolic events (SEE). Each edoxaban group (60 mg and 30 mg) was compared with warfarin for non-inferiority. If non-inferiority versus warfarin was established for the edoxaban 60 mg group, then superiority would be tested. The secondary efficacy objectives were to compare edoxaban to warfarin with regard to:

- Composite of stroke, SEE, and cardiovascular (CV) mortality
- Major adverse cardiovascular event (MACE): a composite of non-fatal MI, non-fatal stroke, non-fatal SEE, and death due to CV cause or bleeding
- Composite of stroke, SEE, and all-cause mortality

3.1 KEY FINDINGS OF EDOXABAN EFFICACY^{9, 10}

The DCRP clinical review of edoxaban found that the results of the primary efficacy analysis on the first adjudicated stroke/SEE modified intent-to-treat (mITT) population, on treatment period were positive and statistically significant for both doses: edoxaban 30 mg: hazard ratio (HR): 1.07 (0.87-1.31) and edoxaban 60 mg: HR: 0.79 (0.63-0.99). Both doses met the pre-specified non-inferiority criteria (with a margin of 1.38) compared to warfarin. Additionally, the ischemic stroke and disabling stroke subcomponents of the primary efficacy analysis were consistent with non-inferior efficacy for the 60 mg edoxaban group. However, in the edoxaban 30 mg (15 mg dose adjustment [DA]) group, results were not favorable for ischemic stroke [HR (95% CI): 1.54

⁷ Edoxaban (NDA 206316) Original Submission ORIG-1, Section 2.5 Clinical Overview-Atrial Fibrillation, dated January 8, 2014 (eCTD Seq. No. 0000)

⁸ Dronedarone was added to the list of P-gp inhibitors requiring dose reduction for the edoxaban study in December 2010 following results of the dronedrone drug-drug interaction study.

⁹ Blank, M. and McDowell, T. Division of Cardiovascular and Renal Products Clinical Review (clinical efficacy) for Edoxaban (NDA 206316) dated October 3, 2014.

¹⁰ Division of Cardiovascular and Renal Products Briefing Package for the October 30, 2014 CRDAC meeting.

(1.25-1.9)] and disabling stroke [HR (95% CI): 1.36 (0.91-2.03)]. For this reason, the Sponsor proposed to carry forth only the 60 mg (30 mg DA) edoxaban regimen to market.

FDA undertook subgroup analysis which identified potential efficacy issues which required further discussion internally, with the Sponsor and during the AC meeting, as cited above in Section 1.2 Regulatory History.

Key efficacy issues identified by the Agency include the following findings:

- Exposure-Response Relationship^{11,12}: An interaction between efficacy results and renal function was identified in a subgroup analysis of edoxaban which resulted in FDA reviewers concluding the following:
 - 1) Patients with normal renal function may benefit from an increase in dose from that studied
 - 2) Increasing exposure in patients with normal renal function to match those in the 60 mg (mild renal insufficiency) group is not expected to increase the risk of life-threatening bleeds beyond that observed for warfarin in the corresponding subgroups
 - 3) In patients with moderate renal insufficiency, a dose adjustment that results in exposure matching to patients with mild renal insufficiency is expected to increase efficacy by decreasing the risk for ischemic stroke and not expected to increase the risk for life threatening bleeds greater than that observed in patients treated with warfarin.

3.2 KEY FINDINGS OF EDOXABAN SAFETY^{13,14}

The primary safety endpoint was major bleeding as adjudicated by the Clinical Events Committee (CEC), with secondary endpoints including the composite of major bleeding and clinically relevant non-major (CRNM) bleeding. Additionally, cases with pre-defined liver function abnormalities and adverse events (AEs) indicating hepatic dysfunction (as described in the CEC charter) were evaluated and adjudicated by independent external hepatic specialists in a blinded manner. Other safety assessments included, but were not limited to, all bleeding (including minor bleeding events), all non-bleeding AEs (including malignancies, bone fractures and all other AEs), and laboratory assessments.

The primary safety data are from two phase 3 trials used to support the AF and DVT/PE indications: ENGAGE AF-TIMI and Hokusai VTE. The reviewer's safety analysis focused on data in ENGAGE AF TIMI, which should allow substantive assessment of the safety of edoxaban in an AF population. ENGAGE-AF TIMI included a total of 21,105 subjects who were randomized with 21,026 subjects having at least on study drug treatment (N = 7002, 7012, and 7012 for the edoxaban 30 mg, edoxaban 60 mg and warfarin groups, respectively).

¹¹ Earp, J. et al. Office of Clinical Pharmacology, Summary of Exposure-Ischemic Stroke/Life-Threatening Bleeding Analyses for SPAF Indications of Edoxaban (NDA 206316) Mid-cycle meeting June 24, 2014

¹² Earp, J. Slide Presentation 'Edoxaban Dosing Considerations Based on Renal Function' from the October 30, 2014 Cardiovascular and Renal Drug Products Advisory Committee meeting

¹³ McDowell, T.Y. Division of Cardiovascular and Renal Products Clinical Review (Clinical Safety) of Edoxaban (NDA 206316) dated October 3, 2014.

¹⁴ Division of Cardiovascular and Renal Products Clinical Team Slide presentation 'How to Approach the Observed Decreased Efficacy of Edoxaban in Subjects with Normal Renal Function

The DCRP clinical review of safety found that edoxaban was favorable to warfarin in major bleeding with or without hemorrhagic stroke (HR 1.24 95% CI:1.02-1.50).

Key safety issues identified include questions surrounding the exposure-response relationship and associated predictions in bleeding risks, along with hepatic abnormalities.

Exposure-Response Relationship and Risk of Bleeding:

According to the efficacy findings and exposure-response analyses discussed above in Section 3.1, there was evidence suggesting that the proposed dose (60 mg) was suboptimal (under-dosed) for subjects with normal renal function. While the efficacy may be attainable by increasing the dose in this subgroup, safety concern with respect to bleeding risk, particularly gastrointestinal (GI) bleeds, has been raised. Per DCRP clinical review of safety, the rate of major bleeding event was markedly decreased among subjects with CrCL \geq 80 mL/min in both treatment groups. These results are expected given that normal renal function subgroup represents younger and healthier subjects. Among subjects with CrCL \geq 80 mL/min, event rates in all categories of major bleeds, including GI major bleeds, were lower in the edoxaban 60 mg group compared with warfarin.

Hepatic Abnormalities

Per DCRP clinical review of safety, pre-defined liver laboratory abnormalities and hepatic cases of special interest (SAEs or AEs leading to study drug interruption/discontinuation) were independently reviewed by two CEC hepatic specialists for adjudication. The percentage of subjects in the edoxaban 30 mg, edoxaban 60 mg and warfarin groups with ALT or AST \geq 3 x upper limit of normal (ULN) was similar (2.5%, 2.6% and 2.5 %, respectively). However, the edoxaban 60 mg had more cases with increased liver enzyme values (subjects with ALT \geq 5 to 10 times ULN and subjects with ALT or AST with \geq 5 to 20 ULN) compared to the warfarin group. The number of subjects with ALT or AST \geq 3 x ULN and beyond was consistently higher in the edoxaban 60 mg group compared with the warfarin group. The number of subjects with combination abnormality seems similar among the treatment groups. The liver laboratory data in combination with the adjudication results demonstrated an imbalance for the edoxaban 60 mg group compared with the warfarin group. Although the imbalance was small, the DCRP clinical reviewer requested a consultation from the Office of Surveillance and Epidemiology (OSE) to comprehensively review and analyze the liver data in both ENGAGEAF TIMI 48 and Hokusai VTE.

The OSE hepatic consult review of the cases of hepatic abnormalities for edoxaban found that “the current data show that edoxaban is unlikely to cause drug-induced liver injury and suggests that edoxaban is not different from warfarin and other approved NOACs with regard to liver toxicity. Furthermore, the fairly frequent elevation of liver transaminases is likely to be associated with an underlying cardiac condition in the AF population.” The OSE consult reviewer additionally provided considerations for labeling of edoxaban to include warnings about elevations in select liver laboratory values, and considerations for periodic monitoring of patients with AF who are initiating therapy on edoxaban.¹⁵ DRISK notes that as labeling negotiations for the AF indication of edoxaban have not yet been finalized, based on conclusions made by DCRP and OSE with regard to hepatic abnormalities, it is likely that this information

¹⁵ Senior, J. Office of Surveillance and Epidemiology (OSE) Hepatology Consultation Review for Edoxaban (NDA 206316) dated September 25, 2014

can be adequately communicated through labeling, without additional risk management considerations.

4 CARDIOVASCULAR AND RENAL DRUGS ADVISORY COMMITTEE MEETING

On October 30, 2014, the Cardiovascular and Renal Drugs AC met to discuss NDA 206316 Edoxaban for the proposed indication of prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

The AC members discussed their interpretation of the primary efficacy endpoint, ischemic stroke and bleeding results in the various subgroups based on renal function; their considerations for a dose higher than 60 mg daily for patients with normal renal function, based on the analyses presented, and major safety and efficacy outcomes in ENGAGE-AF; their considerations for doses of 60 mg and below, or higher doses for patients with normal renal function.

The Committee subsequently voted as follows:

1. Should edoxaban be approved to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation?

Committee Vote Results: YES: 9 NO: 1

If you recommend approval, please vote/discuss options:

- A) Approval of the 60-mg dose for patients with normal or mildly impaired renal function.
- B) Approval of a dose higher than 60 mg for patients with normal renal function.
- C) Approval only for patients with mild and moderate renal impairment.

Committee Vote Results:

OPTION A	OPTION B	OPTION C
5	2	2

5 RISK MANAGEMENT PROPOSED BY THE SPONSOR¹⁶

The Sponsor did not submit a risk mitigation strategy for edoxaban beyond professional labeling and a Medication Guide (MG) in their original submission.

5.1 SPONSOR'S PROPOSED PROFESSIONAL LABELING

Following the AC, and discussions with DCRP, the Sponsor proposed labeling that included a dosing regimen of 30 mg, 60 mg (b) (4) once daily, based on creatinine clearance levels. However, subsequent to additional internal decisions, the Agency determined (b) (4) was not acceptable and therefore currently proposes approving 60mg QD with a limitation of use (b) (4)

In the proposed edoxaban labeling provided in the Sponsor's original submission, the only proposed contraindication is in patients with active pathological bleeding. The Dosage and Administration Section for edoxaban included comprehensive conversion directives for

¹⁶ Edoxaban proposed labeling from the original submission ORIG-1 January 8, 2014. Labeling discussions are currently underway for both DCRP (AF) indication, as well as the DHP indications, in conjunction with the evaluation of NDA 206316.

switching to or from edoxaban and to or from warfarin, oral anticoagulants other than warfarin, low molecular weight heparin and unfractionated heparin. Warnings and Precautions Section for edoxaban included the risk of bleeding, patients with mechanical heart valves, and increased risk of thrombotic events after premature discontinuation. The Adverse Events Section cites bleeding as the most serious adverse event associated with the use of edoxaban.

5.2 SPONSOR’S PROPOSED MEDICATION GUIDE

The Sponsor’s proposed MG contains information that aligns with the proposed edoxaban labeling including information about the serious risk of bleeding seen in patients with AF. These include information on higher risks of bleeding associated with edoxaban use, specific warnings against stopping edoxaban before first talking to the doctor who prescribed the drug, how to take edoxaban, when to call the doctor, along with other information about edoxaban use. Those patients advised against taking edoxaban include only those with certain types of abnormal bleeding. The MG was reviewed under separate cover by the Office of Medical Policy PLT team.¹⁷

6 RISK MANAGEMENT CONSIDERATIONS FOR EDOXABAN

6.1 RISK OF THROMBOTIC EVENTS WHEN DISCONTINUING WITHOUT ADEQUATE ALTERNATIVE ANTICOAGULANT

6.1.1 History of risk management with similar products

Risk management considerations for edoxaban included an evaluation edoxaban in comparison with other approved novel oral anticoagulant (NOAC) and anti-platelet products. The table provided in Appendix A shows the specific risks the REMS for previously approved NOAC products were intended to mitigate. In addition, the table includes information about the REMS goals, REMS elements and whether REMS activities are ongoing or whether the REMS has been released. Released REMS indicate that the Sponsor fulfilled the requirements of the REMS, the Agency determined the REMS met its goal and the REMS was no longer necessary to ensure the benefits of the drug outweigh the risk.

The two NOAC products most similar to edoxaban, Xarelto (rivaroxaban) and Eliquis (apixaban), were approved with REMS to mitigate the increased risk of thrombotic events when discontinuing without an adequate alternative anticoagulant. DCRP’s clinical reviewer states that a distinguishing aspect of the pivotal trial for edoxaban was a transition program that provided a strategy to maintain anticoagulation when patients were transitioned from study drug to warfarin or other anticoagulants after the common study end date. In contrast, the pivotal trials for other NOACs, including Xarelto and Eliquis, a transition program was lacking, resulting in high stroke rates during transition off study drug. Subsequently a communication plan (CP) REMS was found to be necessary for both Xarelto and Eliquis at the time of approval to communicate important directives about conversion to warfarin due to the risk of thrombotic events. Given the comprehensive transition plan included as part of the edoxaban program, specific conversion/transition information will detailed in product labeling, and therefore, would not require added communications measures provided in previous CP REMS for the other NOAC

¹⁷ Mills, S. Office of Medical Policy Division of Patient Labeling Review of Edoxaban NDA 206316 dated January 2, 2015.

products. This information was considered in our evaluation of whether a REMS is necessary for edoxaban for AF, and is discussed further below.

6.1.2 Discussion of risk of thrombotic events when discontinuing

As cited above in Section 6.1.1 and early in the review process¹⁸, risk management for similar NOAC products centered around risk messaging focused on the risk of thromboembolism related to premature discontinuation without adequate anti-coagulation. The risk mitigation strategy to address the risk of thromboembolism included informing healthcare professionals about directives for converting patients to/from NOAC therapy to/from warfarin or other anticoagulants. When evaluating any potential risk management activities for edoxaban, DRISK considered the history of these other similar NOAC products REMS and subsequent fulfillment of these products' REMS activities. These considerations factored into past decisions to eliminate the REMS for these products over the past two years.¹⁹

DRISK considered that if no additional risks were identified for edoxaban, there was no need for a REMS. As noted above, we find that based on the increasing awareness in clinical practice about risks of bleeding, this risk is well known and will continue to be communicated through labeling. Additionally, the edoxaban clinical program, as studied in the ENGAGE-AF TIMI clinical trial, includes a comprehensive conversion program for the appropriate conversion to/from NOAC products to/from to other anti-coagulants. Because other approved NOAC products did not have the same level of detail in their product labeling, their approvals included CP REMS with risk messaging targeting conversion directives to/from other anticoagulants. Edoxaban provides enhanced and specific conversion directives for clinicians to reference in product labeling and therefore, added measures such as a CP REMS are not needed.

6.2 DECREASED EFFICACY (INCREASED THROMBOTIC EVENTS) IN PATIENTS WITH NORMAL RENAL FUNCTION

As discussed above in Section 3.1, and further discussed during the October 30, 2014 AC, there were subsequent issues identified during the review process surrounding renal function effect on efficacy for edoxaban. These findings led to the pathway for the studied 60 mg dose (reduction in dose for severe renal impairment for the AF indication) that proposes a limitation of use in patients with CrCl > (b) (4) due to increased risk of ischemic stroke compared to warfarin (based on DCRP's subgroup analysis of renal function). DRISK agrees that this information is important to communicate to clinicians. However, if edoxaban is used as indicated in patients with CrCl < (b) (4) additional risk mitigation beyond labeling are not necessary at this time. In addition, if edoxaban is used in patients with CrCl > (b) (4) patients will be subject to lack of efficacy rather than increase risk of AEs related to edoxaban.

Based on the issues identified during the DCRP safety and efficacy review of edoxaban, specifically the subgroup analysis findings of the relationship between renal function and efficacy²⁰, and as discussed in this review, labeling for edoxaban includes language in the Boxed

¹⁸ Division of Cardiovascular and Renal Products NDA Filing Meeting for Edoxaban (NDA 206316) for AF, DRISK presentation dated February 14, 2014

¹⁹ Xarelto (rivaroxaban) NDA 202439 REMS eliminated February 12, 2014, Pradaxa (dabigatran etexilate mesylate) NDA 22512 REMS eliminated April 5, 2011 and Brilinta (ticagrelor) NDA 22433 REMS eliminated October 30, 2013. FDA Released REMS Webpage:
<http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm393231.htm>

Warning about reduced efficacy in select patients based on creatinine clearance level. Additionally, related language appears in the Indications and Use, Dosage and Administration, and Warnings and Precautions sections which aligns with DCRP findings and recommendations for edoxaban use.

7 DISCUSSION

DCRP's evaluation of the sponsor's submission found edoxaban to be favorable to warfarin in major bleeding with or without hemorrhagic stroke (HR 1.24 95% CI:1.02-1.50). The AC voted 9/1 in favor of approving edoxaban for the AF indication. Most members opted for approval of the studied 60 mg dose (5), with two members favoring the proposal to approve a higher than studied dose and two members favoring the proposal to approve the studied dose for only renally impaired patients.²¹

DCRP proposes edoxaban for AF at a 60 mg once daily dose (reduced to 30 mg in patients with CrCL 15 to 50 mL/min) with limitations of use. DRISK believes that proposed labeling for the AF indication provides comprehensive directives for clinicians regarding assessing patient creatinine clearance levels, dosing and administration, conversion to/from edoxaban to/from other anti-coagulants, and use in the appropriate patient population for the AF indication. Based on these findings, DRISK believes additional risk management measures beyond labeling are not necessary at this time.

8 CONCLUSION

In conclusion, risk mitigation measures beyond professional labeling are not warranted for edoxaban. Edoxaban has proven efficacy in the treatment of non-valvular atrial fibrillation. The safety profile for edoxaban is comparable to the known safety profile for other approval NOACs. Thus, the benefit-risk profile for edoxaban is acceptable and the risks can be mitigated through professional labeling. If new safety information becomes available that changes the benefit risk profile for edoxaban and warrant further considerations for a REMS, this recommendation should be reevaluated.

²⁰ Blank, M. (efficacy) and McDowell, T. (safety) Review of Clinical Efficacy and Safety for Edoxaban NDA 206316 completed October 9, 2014.

²¹ FDA Cardiovascular and Renal Drugs Advisory Committee October 30, 2014 Meeting Transcripts: <http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/CardiovascularandRenalDrugsAdvisoryCommittee/ucm378911.htm>

Appendix A:

Recently Approved Novel Oral Anticoagulant (NOAC) and Anti-Platelets				
Product	Rivaroxaban	Apixaban	Dabigatran	Ticagrelor
Trade Name	XARELTO	ELIQUIS	PRADAXA	BRILINTA
Approval Date	11/1/2011	12/28/2012	10/19/2010	7/20/2011
Class	Selective Factor Xa Inhibitor	Factor Xa Inhibitor	Direct Thrombin Inhibitor	P2Y12 Platelet Inhibitor
BOXED WARNING	A) Premature discontinuation of Xarelto increases risk of thrombotic events B) Spinal/Epidural Hematomas	A) Premature discontinuation of Eliquis increases risk of thrombotic events B) Spinal/Epidural Hematomas	A) Premature discontinuation of Pradaxa increases risk of thrombotic events B) Spinal/Epidural Hematomas	A) Bleeding Risks B) Aspirin Dose and Brilinta Effectiveness
Labeled RISKS Warnings & Precautions	a) Risk of bleeding: Xarelto can cause serious and fatal bleeding b) Pregnancy related hemorrhage: Use Xarelto with caution in pregnant women due to potential for obstetric hemorrhage and/or emergent delivery. Promptly evaluate signs and symptoms of blood loss. c) Prosthetic heart valves: Xarelto use not recommended.	a) Eliquis can cause serious, potentially fatal bleeding. Promptly evaluate signs and symptoms of blood loss. B) Severe hypersensitivity to Eliquis	a) Bleeding: Pradaxa can cause serious and fatal bleeding b) Bioprosthetic heart valve: Pradaxa use not recommended	a) Brilinta increases the risk of bleeding. B) In Plato, use of Brilinta with maintenance doses of aspirin above 100 mg decreased effectiveness. C) Moderate hepatic impairment: Consider the risk and benefit of treatment, noting probable increase in exposure to ticagrelor d) Dyspnea was reported more frequently with Brilinta than with clopidogrel. Dyspnea resulting from Brilinta is self-limiting. Rule out other causes e) Premature discontinuation increases the risk of myocardial infarction, stent thrombosis, and death
Medication Guide	YES Part of Labeling	YES Part of Labeling	YES Part of REMS	YES Part of REMS
REMS ELEMENTS:	Communication Plan	Communication Plan	Medication Guide only	Communication Plan and Medication Guide
REMS GOAL:	1) To inform healthcare professionals (HCPs) that discontinuing XARELTO without introducing an adequate alternative anticoagulant places nonvalvular atrial fibrillation patients at an increased risk of thrombotic events, including stroke, and to follow recommendations in the US Prescribing Information (USPI) on how to convert nonvalvular atrial fibrillation patients from XARELTO to warfarin or other anticoagulants. 2) To inform nonvalvular atrial fibrillation patients that XARELTO should not be stopped without first informing their healthcare professional as to minimize the risks of post discontinuation thrombotic events.	To inform HCPs about: 1) the increased risk of thrombotic events in patients with nonvalvular atrial fibrillation when discontinuing Eliquis without introducing an adequate alternative anticoagulant 2) the importance of following the recommendations in the USPI on how to convert patients with nonvalvular atrial fibrillation from Eliquis to warfarin or other anticoagulants	The goal of this REMS is to inform patients about the serious risks associated with the use of Pradaxa	1) To inform HCP and patients of the serious risks associated with Brilinta, particularly the increased risk of bleed 2) To inform HCP and patients that the daily maintenance dose of aspirin, co-administered with Brilinta, should not exceed 100 mg
REMS Released (YES/NO)	YES REMS released 2/12/2014	NO CP activities ongoing	YES REMS released 4/5/2011	YES REMS released 10/30/2013

Abbreviations: AF-atrial fibrillation; CP-Communication Plan; D/C-discontinuation; DVT-deep vein thrombosis; HCP-Healthcare Professionals; ICH-Intracranial hemorrhage; N/A-not applicable; P-gp-P-glycoprotein; NME-New Molecular Entity; REMS-Risk Evaluation and Mitigation Strategy; w-with; pts-patients; tx-treatment;

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/s/

CATHY A MILLER
01/05/2015

REEMA J MEHTA
01/06/2015
I concur

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) Review

Date: October 8, 2014

Reviewer(s): Cathy A. Miller, M.P.H., B.S.N.
Risk Management Analyst
Division of Risk Management

Team Leader Kimberly Lehrfeld, Pharm.D., BCPS
Team Lead
Division of Risk Management

Acting Deputy Director Reema Mehta, Pharm.D., M.P.H.
Division of Risk Management

Drug Name(s): SAVAYSA (edoxaban)

Therapeutic Class: Factor Xa Inhibitor

Dosage and Route: 15 mg, 30 mg and 60 mg oral tablets

Application Type/Number: NDA 206316

Submission Number: ORIG-1 Submission Seq. No. 0000 dated 1/8/2014

Applicant/Sponsor: Daiichi-Sankyo, Inc.

OSE RCM #: 2014-65

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1 INTRODUCTION

The purpose of this review is to summarize the Division of Risk Management's (DRISK) current evaluation of the need for a risk evaluation and mitigation strategy (REMS) for Savaysa¹ (edoxaban), new drug application (NDA 206316). The NDA was submitted by Daiichi-Sanyo Pharma Development (Daiichi-Sanyo) and is currently under review by the Division of Cardiovascular and Renal Products (DCRP) for the proposed indication of reduction of the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF). The NDA submission also included a separate proposed indication of treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) (b) (4)

(b) (4) which is under review by the Division of Hematology Products (DHP). The Sponsor did not include a proposed REMS for either indication in their submission.

DRISK's recommendation is to defer the evaluation of the need for a REMS for edoxaban until after the Cardiovascular and Renal Advisory Committee (CRDAC) provides input with regard to the safety and efficacy.

1.1 BACKGROUND

Edoxaban (NDA 206316) is an orally active, selective Factor Xa inhibitor that is being developed as an anticoagulant (b) (4). This review will evaluate the need for a REMS for the proposed indication of reduction in the risk of stroke and system embolism in patients with nonvalvular AF. A separate DRISK review was conducted to evaluate the need for a REMS for the following indications: treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) (b) (4)

(b) (4) DRISK concluded that a REMS was not necessary to ensure the benefits outweighed the risks for the treatment of DVT and PE.

Proposed dosing of edoxaban for the indication of reduction in the risk of stroke and system embolism in patients with nonvalvular AF is 60 mg taken orally once daily. A dose reduction to 30 mg once daily for edoxaban for the AF indication is recommended in patients with one or more of the following:

- (b) (4) (creatinine clearance [CrCL] 15-50 mL/min)
- Low body weight ≤60 kg (132 lbs)
- Concomitant use of P-glycoprotein (P-gp) inhibitors (b) (4)

Specific dosing information is also provided for switching to or from edoxaban for warfarin, oral anticoagulants other than warfarin, low molecular weight heparin (LMWH) and unfractionated heparin. Edoxaban will be available in 15 mg (orange), 30 mg (pink) and 60 mg (yellow) round shaped, film-coated, non-scored tablets.

¹ The proposed Proprietary Name SAVAYSA is currently under review by the Division of Medication Error Prevention and Analysis (DMEPA).

²Yancey, C. Division of Risk Management, Risk Evaluation and Mitigation Strategy (REMS) Review for Savaysa (edoxaban) dated September 17, 2014.

1.2 REGULATORY HISTORY

On January 8, 2014, the Agency received an original NDA from Daiichi-Sanyo for edoxaban for the proposed indications of reduction in the risk of stroke and system embolism in patients with nonvalvular AF. The Sponsor did not propose a REMS.

On June 12, 2014, the internal mid-cycle meeting was held for the edoxaban AF indication. Although efficacy results showed that edoxaban was non-inferior to warfarin in the pivotal ENGAGE-AF trial, there were select key efficacy issues identified.

- An interaction between efficacy results and renal function (subgroup analysis showed that patients with renal impairments had better outcomes than patients with normal renal function); which called the appropriate dose into question.
- Additionally, efficacy findings showed that the Sponsor's dose adjustment (DA) strategy to decrease (by half) the edoxaban dose for subjects with renal insufficiency, low weight and concomitant P-gp inhibitors resulted in a decrease in efficacy in subjects who were dose reduced for low weight and concomitant P-gP inhibition; which called the DA strategy into question.

Key safety findings presented during the mid-cycle meeting included major bleeding, hepatic abnormalities, and worse net clinical benefit for edoxaban (compared to warfarin) among subjects with normal renal function.

On June 18, 2014, a teleconference was held between the edoxaban review team for the AF indication, led by DCRP, and the Sponsor, to provide formal notification of plans to convene a meeting of the Cardiovascular and Renal Drug Products Advisory Committee (CRDAC) to discuss the AF indication portion of the edoxaban NDA. Also discussed with the Sponsor, in the context of the CRDAC plans, were preliminary highlights of findings about the interaction between efficacy results and renal function. DCRP stated that discussions at the AC would likely include these key efficacy findings and the associated benefit-risk assessment of efficacy and safety for edoxaban. The CRDAC is scheduled for October 30, 2014.³

On June 24, 2014, the edoxaban mid-cycle communication meeting/teleconference was held with the Sponsor. All preliminary findings, as cited above and discussed at in the internal mid-cycle meeting, were reviewed with the Sponsor.

On August 6, 2014, DCRP held a face-to-face meeting with the Sponsor. The Sponsor provided preliminary modeling and other analyses (not formally submitted) relevant to discussions surrounding exposure matching for optimal edoxaban dosing as introduced by DCRP at the mid-cycle meeting teleconference.

On August 27, 2014, DCRP held a teleconference with the Sponsor to review issues surrounding the interaction between efficacy and renal function and additional data about exposure matching for optimal edoxaban dosing.

³ [Federal Register Announcement](#) for the October 30, 2014 Cardiovascular and Renal Drugs Advisory Committee Meeting (posted September 17, 2014).

On September 29, 2014, DCRP sent the Sponsor the Late Cycle Meeting background package which included any substantive review issues, in preparation for the scheduled late cycle meeting. DRISK comments provided in the letter included the following:

- ***Atrial Fibrillation (ORIG-1)*** Edoxaban (NDA 206316) is currently under review for the proposed indication of the reduction in the risk of stroke and system embolism in patients with nonvalvular AF. The Division of Risk Management (DRISK) review team for this indication cannot make final determinations about the need for a Risk Evaluation and Mitigation Strategy (REMS) for edoxaban until the risk-benefit profile is further discussed at the October 30, 2014 meeting of the Cardiovascular and Renal Drugs Advisory Committee (AC). Following AC discussions, including the committee's recommendations about the safety and efficacy profile of edoxaban, DRISK will make a recommendation on risk management strategies for the product.
- ***Treatment of deep vein thrombosis and pulmonary embolism (ORIG-2)*** (b) (4)
[REDACTED] No issues that would require a REMS for the VTE indication have been identified to date.

On October 8, 2014, the edoxaban Late Cycle meeting with the Sponsor was held.

2 MATERIALS REVIEWED

2.1 SUBMISSIONS

- Daiichi-Sankyo Original NDA Submission (ORIG-1) for edoxaban (Seq. No. 0000) submitted January 8, 2014

2.2 OTHER MATERIALS INFORMING OUR REVIEW

- Blank, M., Lawrence, J., and McDowell, Z., Division of Cardiovascular and Renal Products (DCRP) Mid-Cycle presentation slides for edoxaban (Clinical, Statistics and Safety), held June 12, 2014 (internal) and June 24, 2014 (teleconference with Daiichi-Sankyo)
- Earp, J., Menon-Anderson, D and Madabushi, R. Office of Clinical Pharmacology Mid-Cycle presentation slides for edoxaban (Clinical Pharmacology and Pharmacometric) held June 12, 2014 (internal) and June 24, 2014 (teleconference with Daiichi-Sankyo)
- Stockbridge, N. Division of Cardiovascular and Renal Products Late Cycle Meeting Background Package for edoxaban dated September 29, 2014
- Blank, M. and McDowell, Z, Division of Cardiovascular and Renal Products, Clinical Review of Safety and Efficacy for edoxaban dated October 3, 2014

3 SUMMARY OF THE EDOXABAN CLINICAL DEVELOPMENT PROGRAM⁴

As described in the Sponsor's original submission, efficacy for edoxaban was evaluated for the AF indication in one Phase 3 pivotal registration study (DU176b C-U301), also known as ENGAGE AF-TIMI 48 (ENGAGE AF). ENGAGE AF was a double-blind, randomized,

⁴ Edoxaban (NDA 206316) Original Submission ORIG-1, Section 2.5 Clinical Overview-Atrial Fibrillation, dated January 8, 2014 (eCTD Seq. No. 0000)

controlled study that included 21,105 subjects with AF treated for a median duration of 2.5 years and followed for a median duration of 2.8 years. The trial evaluated the efficacy and safety of the high and low dosing regimens of edoxaban (edoxaban 60 mg group and edoxaban 30 mg group) administered once daily in comparison to warfarin. In both edoxaban treatment groups, the dose was halved for subjects with moderate renal impairment ($\text{CrCL} \geq 30$ and ≤ 50 mL/min), low body weight (≤ 60 kg), or for subjects receiving concomitant P-glycoprotein (P-gp) inhibitors (verapamil, quinidine, dronedarone⁵), allowing for optimization of the dose at the start of treatment. Increases or decreases in edoxaban doses (decrease from 60 mg to 30 mg and 30 mg to 15 mg, as well as increases from 15 mg to 30 mg and 30 mg to 60 mg) were allowed throughout the study in response to a change in a subject's condition.

The primary efficacy objective of the study was to compare edoxaban to warfarin with regard to the time to first occurrence of a composite primary endpoint of stroke and systemic embolic events (SEE). Each edoxaban group (60 mg and 30 mg) was compared with warfarin for non-inferiority. If non-inferiority versus warfarin was established for the edoxaban 60 mg group, then superiority would be tested. The secondary efficacy objectives were to compare edoxaban to warfarin with regard to:

- Composite of stroke, SEE, and cardiovascular (CV) mortality
- Major adverse cardiovascular event (MACE): a composite of non-fatal MI, non-fatal stroke, non-fatal SEE, and death due to CV cause or bleeding
- Composite of stroke, SEE, and all-cause mortality

3.1 KEY FINDINGS OF EDOXABAN EFFICACY

The DCRP clinical review of edoxaban found that the results of the primary efficacy analysis on the first adjudicated stroke/SEE modified intent-to-treat (mITT) population, on treatment period were positive and statistically significant for both doses: edoxaban 30 mg: hazard ratio (HR): 1.07 (0.87-1.31) and edoxaban 60 mg: HR: 0.79 (0.63-0.99). Both doses met the pre-specified non-inferiority criteria (with a margin of 1.38) compared to warfarin. Additionally, the ischemic stroke and disabling stroke subcomponents of the primary efficacy analysis were consistent with non-inferior efficacy for the 60 mg edoxaban group. However, in the edoxaban 30 mg (15 mg dose adjustment [DA]) group, results were not favorable for ischemic stroke [HR (95% CI): 1.54 (1.25-1.9)] and disabling stroke [HR (95% CI): 1.36 (0.91-2.03)]. For this reason, the Sponsor proposed to carry forth only the 60 mg (30 mg DA) edoxaban regimen to market.⁶

However, FDA undertook subgroup analysis which identified potential efficacy issues which required further discussion internally, with the Sponsor and with the CRDAC.

Key efficacy issues identified by the Agency which will be considered by the CRDAC include discussion of the following:

⁵ Dronedarone was added to the list of P-gp inhibitors requiring dose reduction for the edoxaban study in December 2010 following results of the dronedrone drug-drug interaction study.

⁶ Blank, M. and McDowell, T. Division of Cardiovascular and Renal Products Clinical Review (clinical efficacy) for Edoxaban (NDA 206316) dated October 3, 2014.

- *Exposure-Response Relationship*⁷: An interaction between efficacy results and renal function was identified in a subgroup analysis of edoxaban which resulted in FDA reviewers concluding the following:
 - 1) Patients with normal renal function may benefit from an increase in dose from that studied
 - 2) Increasing exposure in patients with normal renal function to match those in the 60 mg (mild renal insufficiency) group is not expected to increase the risk of life-threatening bleeds beyond that observed for warfarin in the corresponding subgroups
 - 3) In patients with moderate renal insufficiency, a dose adjustment that results in exposure matching to patients with mild renal insufficiency is expected to increase efficacy by decreasing the risk for ischemic stroke and not expected to increase the risk for life threatening bleeds greater than that observed in patients treated with warfarin.

3.2 KEY FINDINGS OF EDOXABAN SAFETY⁸

The primary safety endpoint was major bleeding as adjudicated by the Clinical Events Committee (CEC), with secondary endpoints including the composite of major bleeding and clinically relevant non-major (CRNM) bleeding. Additionally, cases with pre-defined liver function abnormalities and adverse events (AEs) indicating hepatic dysfunction (as described in the CEC charter) were evaluated and adjudicated by independent external hepatic specialists in a blinded manner. Other safety assessments included, but were not limited to, all bleeding (including Minor bleeding events), all non-bleeding AEs (including malignancies, bone fractures and all other AEs), and laboratory assessments.

The primary safety data are from two phase 3 trials used to support the AF and DVT/PE indications: ENGAGE AF and Hokusai VTE. The reviewer's safety analysis focused on data in ENGAGE AF, which should allow substantive assessment of the safety of edoxaban in an AF population. ENGAGE AF included a total of 21,105 subjects who were randomized with 21,026 subjects having at least on study drug treatment (N = 7002, 7012, and 7012 for the edoxaban 30 mg, edoxaban 60 mg and warfarin groups, respectively).

The DCRP clinical review of safety found that edoxaban was favorable to warfarin in major bleeding with or without hemorrhagic stroke (HR 1.24 95% CI:1.02-1.50).

However, there were safety concerns identified by DCRP. Key safety issues identified include questions surrounding the exposure-response relationship and associated predictions in bleeding risks, along with hepatic abnormalities.

Exposure-Response Relationship and Risk of Bleeding:

According to the efficacy findings and exposure-response analyses discussed above, there was evidence suggesting that the proposed dose (60 mg) was suboptimal (under-dosed)

⁷ Earp, J. et al. Office of Clinical Pharmacology, Summary of Exposure-Ischemic Stroke/Life-Threatening Bleeding Analyses for SPAF Indications of Edoxaban (NDA 206316) Mid-cycle meeting June 24, 2014

⁸ McDowell, T.Y. Division of Cardiovascular and Renal Products Clinical Review (Clinical Safety) of Edoxaban (NDA 206316) dated October 3, 2014.

for subjects with normal renal function. While the efficacy may be attainable by increasing the dose in this subgroup, safety concern with respect to bleeding risk, particularly gastrointestinal (GI) bleeds, has been raised. Per DCRP clinical review of safety, the rate of major bleeding event was markedly decreased among subjects with CrCL \geq 80 mL/min in both treatment groups. These results are expected given that normal renal function subgroup represents younger and healthier subjects. Among subjects with CrCL \geq 80 mL/min, event rates in all categories of major bleeds, including GI major bleeds, were lower in the edoxaban 60 mg group compared with warfarin. Modeling and analyses suggest that edoxaban 90 mg is likely to cause more major GI bleeds compared with warfarin in subjects with normal renal function. However, the hazard ratio of GI bleeds with edoxaban 90 mg compared with warfarin in subjects with normal renal function would probably not be much different or likely less than what was observed in subjects with mild renal impairment treated with edoxaban 60 mg. Considering that the absolute risk in major GI bleeds is very low in subjects with normal renal function, there is assurance that the overall bleeding risk profile is likely to be acceptable with a higher dose, however, an appropriate dose would still need to be identified to balance efficacy and safety in the subgroup, and DCRP has advised that this issue be considered further by the CRDAC.

Hepatic Abnormalities

Per DCRP clinical review of safety, pre-defined liver laboratory abnormalities and hepatic cases of special interest (SAEs or AEs leading to study drug interruption/discontinuation) were independently reviewed by two CEC hepatic specialists for adjudication. The percentage of subjects in the edoxaban 30 mg, edoxaban 60 mg and warfarin groups with ALT or AST \geq 3 x upper limit of normal (ULN) was similar (2.5%, 2.6% and 2.5 %, respectively). However, the edoxaban 60 mg had more cases with extremely high liver enzyme values (subjects with ALT \geq 5 to 10 times ULN and subjects with ALT or AST with \geq 5 to 20 ULN) compared to the warfarin group. The number of subjects with ALT or AST \geq 3 x ULN and beyond was consistently higher in the edoxaban 60 mg group compared with the warfarin group. The number of subjects with combination abnormality seems similar among the treatment groups. The liver laboratory data in combination with the adjudication results revealed slightly worse profile for the edoxaban 60 mg group compared with the warfarin group. Although the imbalance was small, the DCRP clinical reviewer requested a consultation from the Office of Surveillance and Epidemiology to comprehensively review and analyze the liver data in both ENGAGEAF-TIMI 48 and Hokusai VTE.

4 RISK MANAGEMENT PROPOSED BY THE SPONSOR

The Sponsor did not submit a risk mitigation strategy for edoxaban beyond professional labeling and a Medication Guide (MG).

4.1 SPONSOR'S PROPOSED PROFESSIONAL LABELING⁹

In the proposed edoxaban labeling, the only proposed contraindication is in patients with active pathological bleeding. The Warnings and Precautions Section for edoxaban included the risk of bleeding, patients with mechanical heart valves, and increased risk of thrombotic events after premature discontinuation. The Adverse Events Section cites bleeding as the most serious adverse event associated with the use of edoxaban. Renal impairment and hepatic impairment are also identified in the Use in Specific Populations Section of the label. Dose reduction is advised for patients with moderate to severe renal impairment. Edoxaban is not recommended for patients with severe hepatic impairment or hepatic disease associated with intrinsic coagulation abnormalities.

4.2 SPONSOR'S PROPOSED MEDICATION GUIDE

The Sponsor's proposed MG contains information that aligns with the proposed edoxaban labeling including information about the increased risks associated with patients with AF. These include information on higher risks of bleeding associated with edoxaban use, specific warnings against stopping edoxaban before first talking to the doctor who prescribed the drug, how to take edoxaban, when to call the doctor, along with other information about edoxaban use. Those patients advised against taking edoxaban include only those with certain types of abnormal bleeding.

5 RISK MANAGEMENT CONSIDERATIONS FOR EDOXABAN

5.1 HISTORY OF RISK MANAGEMENT WITH SIMILAR PRODUCTS

Risk management considerations for edoxaban include an evaluation of trends with other approved novel oral anticoagulant (NOAC) and anti-platelet products. The table provided in Appendix A shows the specific risks the REMS for previously approved NOAC products were intended to mitigate. In addition, the table includes information about the REMS for these products, including risks associated with the products, REMS goals and whether REMS activities are ongoing or the REMS has been released. Released REMS indicate that the Agency determined the REMS met its goal either through completion of elements of the REMS (i.e. communication plan) or a general awareness that the risk of the drug can adequately be communicated through labeling, including a MG.

We note the two NOAC products most similar to edoxaban, Xarelto (rivaroxaban) and Eliquis (apixaban), share the same risk messaging in their respective REMS about increased risk of thrombotic events when discontinuing without an adequate alternative anticoagulant. DCRP provided clarity in their clinical review of edoxaban, about these risks in the context of converting to other anticoagulants. DCRP states that a distinguishing aspect of the pivotal trial for edoxaban was a transition program that provided a strategy to maintain anticoagulation when patients were transitioned from study drug to warfarin or other anticoagulants after the common study end date.

⁹ Edoxaban proposed labeling from the original submission ORIG-1 January 8, 2014. Labeling discussions are currently underway for both DCRP (AF) indication, as well as the DHP indications, in conjunction with the evaluation of NDA 206316.

However, in the pivotal trials for other NOACs, including Xarelto and Eliquis, a transition program was lacking, resulting in high stroke rates during transition off study drug. Subsequently a communication plan (CP) REMS was found to be warranted for both Xarelto and Eliquis at the time of approval to communicate important directives about conversion to warfarin due to the risk of thrombotic events. Given the comprehensive transition plan included as part of the edoxaban program, specific conversion/transition information will likely be included as part of product labeling. While the degree to which that information would warrant additional risk messaging as part of a REMS is unlikely, labeling for the AF indication has not yet been finalized and therefore, our considerations are preliminary at this time.

5.2 UNDETERMINED INDICATED POPULATION

In determining if a REMS should be required, the agency must consider the following factors:

- (A) The estimated size of the population likely to use the drug involved.
- (B) The seriousness of the disease or condition that is to be treated with the drug.
- (C) The expected benefit of the drug with respect to such disease or condition.
- (D) The expected or actual duration of treatment with the drug.
- (E) The seriousness of any known or potential AEs that may be related to the drug and the background incidence of such events in the population likely to use the drug.
- (F) Whether the drug is a new molecular entity.

For edoxaban, factors A, C and E above can only be evaluated if the indicated patient population is known and characterized. However, at this time, the indicated patient population for edoxaban has not been identified.

Each factor is discussed individually below.

❖ Estimated Size of the Population Likely to Use the Drug Involved

As discussed above in Section 3.1, an interaction between efficacy results and renal function was identified in a subgroup analysis of edoxaban. This analysis calls into question which patients may benefit most from the drug based on renal function and what dose provides the most benefit without compromising the safety profile.

It is not possible to estimate the size of the population likely to use the drug since the indicated size of the population that may be exposed to edoxaban (i.e. all patients with nonvalvular AF or select subgroups of patients based on renal function) is unknown.

❖ Expected Benefit of the Drug with Respect to such Disease or Condition

As cited above, the subgroup analyses conducted by the Office of Clinical Pharmacology¹⁰ indicated that patients with normal renal function may benefit from a dose higher than studied. Discussion surrounding this analysis brings into

¹⁰ See Summary of Clinical Pharmacology section for complete review of Edoxaban Modeling and Simulation Exposure-Response Efficacy and Safety Analyses for the Prevention of Stroke and Systemic Embolism in Patients with Nonvalvular Atrial Fibrillation.

question whether the studied dose provides the maximum benefit-risk profile for these patients, or whether an alternate dose could provide increased benefit without compromising the safety profile.

It is not possible to evaluate the overall expected benefit of the drug with respect to such disease or condition since questions surrounding the indicated patient population are still being considered.

❖ **Seriousness of Any Known or Potential Adverse Events Related to the Drug and Background Incidence of Such Events in the Population Likely to Use the Drug**

It is not possible to evaluate the background incidence of AEs in the population likely to use the drug since the indicated patient population is unknown.

In conclusion, until the indicated patient population is determined, which requires input from the CRDAC, a full evaluation of the need for a REMS cannot be made.

5.3 HEPATIC ABNORMALITIES

DCRP concluded in their review of safety for edoxaban, referencing Dr. John Senior's OSE hepatic consult review of the cases of hepatic abnormalities for edoxaban, "the current data show that edoxaban is unlikely to cause drug-induced liver injury and suggests that edoxaban is not different from warfarin and other approved NOACs with regard to liver toxicity. Furthermore, the fairly frequent elevation of liver transaminases is likely to be associated with an underlying cardiac condition in the AF population." The OSE consult reviewer additionally provided considerations for labeling of edoxaban to include warnings about elevations in select liver laboratory values, and considerations for periodic monitoring of patients with AF who are initiating therapy on edoxaban. DRISK notes that labeling negotiations for the AF indication of edoxaban have not yet commenced, however, based on conclusions made by DCRP and OSE with regard to hepatic abnormalities, it is likely that this information can be adequately communicated through labeling, without additional risk management considerations.

6 SUMMARY

Edoxaban was found to be non-inferior to warfarin on safety and efficacy, however, questions remain surrounding the exposure-response relationships and potential novel dose recommendations that may result in increased efficacy and still preserve the safety profile for the drug. DCRP is requesting the CRDAC discuss these issues and make recommendations. Decisions about these issues will play a pivotal role in informing which risk management strategies are necessary to assure the safe use of the product in the intended patient population.

7 CONCLUSION

DRISK defers further comment at this time on the appropriate risk management strategy for edoxaban (NDA 206316) indicated for the reduction of the risk of stroke and systemic embolism in patients with nonvalvular AF. A complete evaluation of the need for a REMS for edoxaban will be undertaken by DRISK after key decisions are made

with regard to the safety, efficacy and the indicated patient population for edoxaban for the AF indication.

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Product	Rivaroxaban	Apixaban	Dabigatran	Ticagrelor
Trade Name	XARELTO	ELIQUIS	PRADAXA	BRILINTA
Approval Date	11/1/2011	12/28/2012	10/19/2010	7/20/2011
Class	Selective Factor Xa Inhibitor	Factor Xa Inhibitor	Direct Thrombin Inhibitor	P2Y12 Platelet Inhibitor
BOXED WARNING	A) Premature discontinuation of Xarelto increases risk of thrombotic events B) Spinal/Epidural Hematomas	A) Premature discontinuation of Eliquis increases risk of thrombotic events B) Spinal/Epidural Hematomas	A) Premature discontinuation of Pradaxa increases risk of thrombotic events B) Spinal/Epidural Hematomas	A) Bleeding Risks B) Aspirin Dose and Brilinta Effectiveness
Labeled RISKS Warnings & Precautions	a) Risk of bleeding: Xarelto can cause serious and fatal bleeding b) Pregnancy related hemorrhage: Use Xarelto with caution in pregnant women due to potential for obstetric hemorrhage and/or emergent delivery. Promptly evaluate signs and symptoms of blood loss. c) Prosthetic heart valves: Xarelto use not recommended	a) Eliquis can cause serious, potentially fatal bleeding. Promptly evaluate signs and symptoms of blood loss. B) Severe hypersensitivity to Eliquis	a) Bleeding: Pradaxa can cause serious and fatal bleeding b) Bioprosthetic heart valve: Pradaxa use not recommended	a) Brilinta increases the risk of bleeding. B) In Plato, use of Brilinta with maintenance doses of aspirin above 100 mg decreased effectiveness. C) Moderate hepatic impairment: Consider the risk and benefit of treatment, noting probable increase in exposure to ticagrelor d) Dyspnea was reported more frequently with Brilinta than with clopidogrel. Dyspnea resulting from Brilinta is self-limiting. Rule out other causes e) Premature discontinuation increases the risk of myocardial infarction, stent thrombosis, and death
Medication Guide	YES Part of Labeling	YES Part of Labeling	YES Part of REMS	YES Part of REMS
REMS ELEMENTS:	Communication Plan	Communication Plan	Medication Guide only	Communication Plan and Medication Guide
REMS GOAL:	1) To inform healthcare professionals (HCPs) that discontinuing XARELTO without introducing an adequate alternative anticoagulant places nonvalvular atrial fibrillation patients at an increased risk of thrombotic events, including stroke, and to follow recommendations in the US Prescribing Information (USPI) on how to convert nonvalvular atrial fibrillation patients from XARELTO to warfarin or other anticoagulants. 2) To inform nonvalvular atrial fibrillation patients that XARELTO should not be stopped without first informing their healthcare professional as to minimize the risks of post discontinuation thrombotic events.	To inform HCPs about: 1) the increased risk of thrombotic events in patients with nonvalvular atrial fibrillation when discontinuing Eliquis without introducing an adequate alternative anticoagulant 2) the importance of following the recommendations in the USPI on how to convert patients with nonvalvular atrial fibrillation from Eliquis to warfarin or other anticoagulants	The goal of this REMS is to inform patients about the serious risks associated with the use of Pradaxa	1) To inform HCP and patients of the serious risks associated with Brilinta, particularly the increased risk of bleed 2) To inform HCP and patients that the daily maintenance dose of aspirin, co-administered with Brilinta, should not exceed 100 mg
REMS Released (YES/NO)	YES REMS released 2/12/2014	NO CP activities ongoing	YES REMS released 4/5/2011	YES REMS released 10/30/2013
Abbreviations: AF-atrial fibrillation; CP-Communication Plan; D/C-discontinuation; DVT-deep vein thrombosis; HCP-Healthcare Professionals; ICH-intracranial hemorrhage; N/A-not applicable; P-gp-P-glycoprotein; NME-New Molecular Entity; REMS-Risk Evaluation and Mitigation Strategy; w-with; pts-patients; tx-treatment;				

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/s/

CATHY A MILLER
10/08/2014

REEMA J MEHTA
10/08/2014

CYNTHIA L LACIVITA
10/09/2014
Concur

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management**

Risk Evaluation and Mitigation Strategy (REMS) Review

Date: September 17, 2014

Reviewer: Carolyn L. Yancey, M.D., Senior Medical Officer, Division of Risk Management (DRISK)

Team Leader: Doris Auth, Pharm. D., DRISK

Acting Division Director: Cynthia LaCivita, Pharm. D., DRISK

Subject: Evaluation to determine whether a REMS is necessary to ensure that the benefits of edoxaban tosylate oral tablets outweigh the risks

Drug Name: SAVAYSA (edoxaban tosylate) Oral Tablet

Therapeutic Class: Selective Inhibitor of Factor Xa

Form and Dosage: Oral tablets: 15 mg, 30 mg, 60 mg dose, once daily

Office of New Drugs: Division of Hematology Products

Application Type/Number: NDA 206-316, Submissions Original-2 (b) (4)

Applicant: Daiichi Sankyo Pharma (Daiichi)

OSE RCM #: 2014-58
2014-65

1 INTRODUCTION

This Division of Risk Management (DRISK) review evaluates whether a risk evaluation and mitigation strategy (REMS) is needed for Savaysa (edoxaban tosylate, as edoxaban) proposed as an oral tablet under the New Drug Application (NDA) 206-316, submitted to the Division of Hematology Products (DHP) as Original (ORIG)-2, proposed for the treatment of adult patients with deep vein thrombosis (DVT) and pulmonary embolism (PE) who have been treated with a parenteral anti-coagulant for 5 to 10 days. (b) (4)

This NDA was received by both the Division of Cardiovascular and Renal Products (DCRP) and the DHP on January 8, 2014. The applicant did not propose a risk management plan (RMP) or REMS for any of the (b) (4) proposed treatment indications. The Prescription Drug User Fee Act (PDUFA) goal date for NDA 206-316 is January 8, 2015.

2 BACKGROUND

Edoxaban (DU-176b) is a proposed fourth-in-class, new molecular entity (NME), novel oral anticoagulant (NOAC) drug product that is a selective inhibitor of Factor Xa (FXa).² Coagulation is defined as the formation of fibrin by a series of linked enzymatic reactions in which each reaction product converts the subsequent inactive zymogen into an active serine protease.³ The FXa is the serine protease located in the final common pathway of the coagulation cascade. By reducing FXa in the coagulation cascade, thrombin production is reduced and clotting time is prolonged, which in-turn, reduces the risk of formation or provoked thrombus formation.⁴ See the **Appendix**, to this review, **Figure 1** Blood Coagulation Cascade and Site of Action of Anticoagulants.

Approximately 35% of an administered dose of edoxaban is cleared via renal excretion. The remaining drug product is metabolized and eliminated via biliary/intestinal excretion. The non-renal elimination includes unchanged edoxaban and is theoretically linked to the potential risk for gastrointestinal bleeding events.²

Edoxaban is currently under clinical trial investigation in the United States (US) [edoxaban studies submitted in this NDA] and the European Union (EU). Edoxaban was approved in Japan as Lixiana on April 22, 2011. See **Section 2.1 Regulatory History** for

¹ NDA 206-315, ORIG-1, edoxaban is proposed to reduce the risk of stroke and SE in adult patients with non-valvular AF (filed with the DCRP on January 8, 2014).

² NDA 206-316 Savaysa (edoxaban) proposed labeling per the DHP, Section 12.1 Mechanism of Action, page 19. Confirmed language with Saleh Ayache, M.D., DHP Clinical Reviewer and Kathy Robie-Shu, M. D., DHP Team Leader. Labeling, Section 12. 1 Mechanism of Action (MOA) for edoxaban is revised per the DHP for consistency with the approved NOAC drug product labeling.

³ J. E. Freedman, J Loscalzo. Chapter 117. Arterial and Venous Thrombosis, Harrison's Principles of Internal Medicine, 18th Ed, Vol 1. page 986-987.

⁴ Mid-Cycle slides from DHP /DCRP and proposed edoxaban labeling Section 12. Clinical Pharmacology

brief comment on the Japanese edoxaban studies in patients with severe renal impairment that are used as supportive data to the Hokusai-VTE study).

In non-clinical studies, equivalent doses of edoxaban ≤ 60 mg (the proposed maximum clinical dose, once daily) were evaluated by the applicant. Edoxaban was not carcinogenic when administered to mice and rats (by oral gavage) daily up to 104 weeks. The highest dose tested (500 mg/kg/day in male and female mice) was 3 and 6 times, respectively, the human exposure (AUC) at the maximum recommended human clinical dose (MRHD) of 60 mg/day. Edoxaban and its human-specific metabolite, M-4, showed positive results in *in vitro* chromosomal aberration tests but were negative in *in vitro* non-clinical genotoxicity studies. Edoxaban is neither mutagenic or clastogenic based on the weight of evidence submitted by the applicant and confirmed by Baichun Yang, Ph.D., Division of Hematology and Oncology Toxicology (DHOT), the DCRP. Edoxaban showed no effects on fertility and early embryogenic development (at doses of up to 1,000 mg/day in rats (162 times the MRHD of 60 mg/day)).⁵ Edoxaban is proposed as Pregnancy C.

Proposed Formulation and Dosage

The proposed, to-be-marketed formulation and strength for edoxaban is an oral tablet (15 mg, 30 mg and 60 mg). The recommended dose is 60 mg administered once daily (b) (4) The reduced 30 mg dose is proposed for patients with:

- (b) (4) [Creatinine Clearance (CrCL) 15-50 mL/min]
- Low body weight ≤ 60 kilograms (kg) (132 lbs)
- Concomitant use of P-glycoprotein (P-gp) inhibitors (b) (4) ²

Venous Thromboembolic Disease

Coagulation is the process by which thrombin is activated and soluble plasma fibrinogen is converted into insoluble fibrin (the clot). This sequence of events occurs in normal hemostasis and in pathophysiologic events that cause development of venous thrombosis (VT).²

The primary forms of VT are DVT in the extremities and with subsequent embolization to the lungs (PE) collectively termed venous thromboembolic disease. Venous thrombosis may be secondary to heritable and/or acquired causes.² See the **Appendix**, to this review, **Table 1**. Acquired Causes of Venous Thrombosis.

Among new cases estimated to be $> 200,000$ per year, 30% of these patients die within 30 days and one-fifth experience sudden death secondary to PE. Another 30% of these cases go on to develop recurrent VT over the next 10 years.² Data from the Atherosclerosis Risk in Communities (ARIC) Study⁶, sponsored by the National Heart, Lung and Blood

⁵ See Non-Clinical Review for Edoxaban written by Shwu-Luan Lee, Ph. D. and labeling discussed with Baichun Yang, Ph. D., DHOT, for the DHP

⁶ Collaborative Studies Coordinating Center, Dept of Biostatistics, Gillings School of Global Public Health at the University of North Carolina at Chapel Hill: The ARIC Study is a prospective epidemiologic study conducted in four United States communities. This study is designed to investigate the causes of atherosclerosis and its clinical outcomes, and variation in cardiovascular risk factors, medical care and

Institute (NHLBI), reported a 9%, 28-day fatality rate from DVT, and a 15% fatality rate from PE. In the setting of cancer, a PE has a worse fatality rate of 25%.

Armamentarium of Therapy for Venous Thromboembolism

Antithrombotic drugs are used for the prevention and treatment of thrombosis. Targeting the components of thrombi, three agents include: (1) anti-platelet drugs, (2) anticoagulants, and (3) fibrinolytic agents. Anticoagulants are the mainstay of prevention and treatment of VTE because fibrin is the predominant component of venous thrombi. Antiplatelet drugs are less effective than anticoagulants in this setting because of the limited platelet content of venous thrombi. Fibrinolytic therapy is used in selected patient with venous VTE.⁷

A water-soluble vitamin K antagonist initially developed as a rodenticide, warfarin is the coumarin derivative most often prescribed in North America. Like other vitamin K antagonists, warfarin is an anticoagulant which interferes with the synthesis of the vitamin K-dependent clotting proteins, which include prothrombin (Factor II) and factors VII, IX and X.⁸ However, the management of warfarin is complicated by the delayed onset of the anticoagulant effect, a narrow therapeutic index that requires close laboratory monitoring for the desired anticoagulant effect and frequent dose adjustments, variable pharmacologic response, and frequent dose-adjustments with drug and food-interactions. Consistent with the risks associated with use of the NOACs, warfarin therapy is associated with serious risks including major and clinically relevant non-major bleeding (CRNM) bleeding events.⁹

Current medical treatment options for patients with thrombotic events (specifically, DVT and PE) include four FDA approved and marketed NOAC drug products:

- **Xarelto (rivaroxaban)** is an inhibitor of FXa indicated for treatment of DVT and prophylaxis of DVT.
- **Eliquis (apixaban)** is an inhibitor of FXa indicated for prophylaxis of DVT.
- **Pradaxa (dabigatran)** is a direct thrombin inhibitor indicated for prophylaxis of DVT.
- **Brilinta (ticagrelor)** is a P2Y12 platelet inhibitor that does not include an indication for DVT or PE.

disease by race, gender, location and date. ARIC includes two parts: Cohort Component and the Community Surveillance Component. The Cohort Component began in 1987 and each ARIC field center recruited 4,000 individuals aged 45-64 years from a defined population in their community to receive examinations, including medical, social and demographic data. In the Community Surveillance Component, the four communities are investigated to determine the long-term trends in hospitalized myocardial infarction (MI) and coronary artery heart disease (CHD) deaths in approximately 470,000 men and women aged 35-84 years of age.

⁷ Chapter 118, “Antiplatelet, anticoagulant, and Fibrinolytic Drugs” by Jeffrey I. Weitz, M.D., 18th Ed. Harrison’s Principles of Internal Medicine by DL Longo, AS Fauci, DL Kasper, SL Hauser, JL Jameson, and J Loscalzo, Vol 1, 2012, page 988.

⁸ As above, in reference 9, page 998, Warfarin.

⁹ NDA 206-316, Edoxaban, GS, Module 2.5 Clinical Overview, page 12

The serious risk of bleeding appears in the Warnings and Precautions Section of rivaroxaban, apixaban and ticagrelor. See Section 4. Discussion for comments on the serious risk of bleeding with NOACs compared with edoxaban.

Three of the four NOAC drug products have been released from the requirement for a REMS. Eliquis (apixaban) has ongoing dissemination of educational materials that focus on communicating the risk of increased thrombotic events, including stroke, in patients with non-valvular atrial fibrillation (AF) when discontinuing Eliquis without introducing an adequate alternative anticoagulant. See the **Appendix**, to this review, **Table 2**. Novel Oral Anticoagulant Products, that includes the indications, labeled safety risks, and current risk management.

Risk Management Plan

As cited in the **Introduction** of this review, the applicant did not submit a proposed RMP or proposed REMS for edoxaban for any of the (b) (4) proposed indications. The applicant includes benefit and risk discussion in the NDA 206-316 submission (Module 2.5 Clinical Overview for VT).

Generic Products for the Treatment of Venous Thromboembolism

The FDA, the Office of Generic Drugs, is not aware of submission of an abbreviated NDA (ANDA) for any of the three NOAC drug products approved for the treatment of DVT and/or PE (or for the reduction of the risk of stroke and SE in patients with non-valvular AF). (b) (4)

Advisory Committee Meeting on Edoxaban

The DHP determined that the clinical efficacy and safety data proposed for the treatment of DVT and of PE will not require an advisory committee meeting during this review cycle.¹⁰

A Cardiovascular and Renal Drug Advisory Committee Meeting (CRDAC) Meeting will be convened on October 30, 2014 to discuss Savaysa (edoxaban), NDA 206-316, proposed to reduce the risk of stroke and systemic embolism in patients with non-valvular AF (ORIG-1 submission). The CRDAC will focus on the potential need, in patients with normal renal function and non-valvular AF, to require a higher dose of edoxaban (90 mg) to achieve efficacy than was studied in the clinical development program (60 mg and 30 mg). The discussion will include clinical pharmacology comparability data, population pharmacokinetic (PK) modeling to predict clinical response with 90 mg of edoxaban, as well as clinical efficacy and safety data in patients with non-valvular AF treated with edoxaban, 60 mg and 30 mg.

¹⁰ NDA 206-316, ORIG-2 is proposed for the treatment of DVT and PE (DHP (b) (4)

2.1 Regulatory History

The regulatory history for NDA 206-316 for edoxaban for VTE in the DHP follows:

- May 27, 2004: The original investigational new drug (IND) 077-254 was initiated for proposed treatment (b) (4) of VTE (DHP). The DHP is not aware of any other indications for edoxaban under IND application beyond the proposed indication in the DCRP under IND 063-266 (non-valvular AF).
- April 22, 2011: Lixiana® (edoxaban) was approved in Japan (15 mg and 30 mg oral once daily) for prevention of VTE in adult patients undergoing total knee replacement, total hip replacement or hip fracture surgery. Supportive studies with edoxaban in the Japanese patients with severe renal impairment are submitted to NDA 206-316, the Hokusai study. The Hokusai study had too few patients with severe renal impairment to support a meaningful evaluation. The applicant claims that the Japanese post-marketing safety data, received to-date, is consistent with the known safety profile of edoxaban and no new safety concerns are reported.¹¹
- November 13, 2012: Type C, Pre-NDA Meeting for edoxaban. There was no discussion of a REMS or risk management in the Meeting Minutes plan.
- October 24, 2013: The applicant's request for a waiver and deferral for pediatric studies under IND 077-254 (PE) and 063-266 (VTE), edoxaban, were accepted by the Agency based on agreement with the proposed Initial Pediatric Study (iPSP) and final agreed with the Pediatric Study Plan (PSP).
- January 8, 2014: The applicant submitted the NDA 206-316 to the Agency with (b) (4) proposed indications (see the **Introduction**, in this review, for details).
- May 8, 2014: The applicant submitted the 120-Day Safety Update Report to the Agency under NDA 206-316.

2.2 Materials Reviewed

- January 8, 2014: NDA 206-316, edoxaban with (b) (4) proposed indications:
 - ORIG-1, proposed to reduce the risk of stroke and systemic embolism (SE) in patients with non-valvular AF.
 - ORIG-2, proposed for the treatment of DVT and PE.

(b) (4)

- May 8, 2014: NDA 206-316, Edoxaban, 120-Day Safety Update Report (SUR) with safety data collected up to the cut-off date of December 31, 2013.
- May 16, 2014: NDA 206-316, Edoxaban Mid-Cycle Meeting slides by Saleh Ayache, M. D., Clinical Reviewer, DHP; Melanie Blank, M. D., Clinical Efficacy Reviewer

¹¹ NDA 206-316, ORIG-1, Edoxaban, GS, Module 2.7.4 Clinical Safety, Subsection 6.6 Safety Assessment, page 184 of 227 (data on DVT, PE, and AF are located in submission ORIG-1, GS)

for Edoxaban, DCRP; and Tzu-Yu McDowell, M. D., Clinical Safety Reviewer for Edoxaban, DCRP.

- May 19, 2014: Pradaxa (dabigatran) - FDA Drug Safety Communication: Lower Risk Stroke and Death, but Higher Risk for GI Bleeding Compared to Warfarin
- August 4, 2014: Consult on the Hepatic Effects of Savaysa (edoxaban) in non-valvular AF, DVT and PE, written by John R. Senior, MD, Associate Director of Science, Office of Pharmacovigilance and Epidemiology (OPE)
- August 19, 2014: Pharmacology - Toxicology Review written by Shwu-Luan Lee, Ph.D. Division of Hematology and Oncology Toxicology (DHOT) for the DHP.
- August 21, 2014: Memorandum - Risk Assessment for Edoxaban Tablets from the Drug Quality Assessment Division II, written by Janice Brown, M.S., CMC Lead, Ali Al-Hakim, Ph.D.
- September 2, 2014: Most recent revisions on the proposed edoxaban labeling from the DHP.
- September 9, 2014: Clinical Review for Edoxaban in VTE (DVT and PE) by Saleh Ayache, MD, DHP.

3 OVERVIEW OF THE CLINICAL DEVELOPMENT PROGRAM

The efficacy and safety of edoxaban 60 mg (including a pre-specified 30 mg dose adjustment regimen), proposed for the treatment of DVT and of PE (b) (4) is based the single pivotal, P-3 clinical trial, the Hokusai VTE study (U305). In the combined edoxaban clinical development program, a second pivotal, P3 study, the Engage study (submitted to the DCRP), supports the proposed treatment to reduce the risk of stroke and SE in patients with non-valvular AF.¹²

HOKUSAI Study in Venous Thromboembolism

The Hokusai study is a multi-national (37 countries), multi-center (439 investigative centers), randomized (R), double-blind (DB), matching-placebo (PBO), parallel group (PG), non-inferiority study design comparing the efficacy and safety of edoxaban 60 mg orally, once daily, to warfarin for patients with acute symptomatic VTE confirmed at baseline by appropriate diagnostic imaging. This study evaluates efficacy and safety of low molecular weight heparin (LMWH)/edoxaban versus (vs.) LMWH/warfarin in patients with symptomatic DVT and/or PE.

Adult male or female patients with acute, symptomatic DVT involving the popliteal, femoral or iliac veins, or PE requiring anticoagulant therapy were eligible for enrollment in the Hokusai study. An independent Data Monitoring Committee (DMC) reviewed and

¹² The clinical data and comments in Section 3, in this review, have been discussed and agreed with by the Clinical Reviewer for Edoxaban, Saleh Ayache, MD, DHP. See Section 2.2 Materials Reviewed, in this review.

monitored this study data in an unblinded manner during the study. Brief summary of the study follows:

- A total of 8,292 patients (59% with DVT only; 41% with PE with or without DVT) were randomized 1:1 to receive edoxaban 60 mg once daily or warfarin (titrated to an International Normalized Ratio (INR)¹³ of 2.0-3.0). A total of 8,240 patients received study drug for up to 12 months.
- Both patient groups received initial heparin therapy with LMWH or unfractionated heparin for at least 5 days (median edoxaban 60 mg group was 7 days, warfarin group was 8 days) and until the INR was ≥ 2.0 on two measurements. Warfarin patients were started concurrently with initial heparin therapy, and edoxaban patients were started after discontinuation of initial heparin.
- Patients with body weight ≤ 60 kg (132 lbs), CrCL ≥ 30 to ≤ 50 mL/min, or concomitant use of the pre-specified P-gp inhibitors (verapamil, quinidine, dronedarone) received a reduced 30 mg edoxaban dose (or matching PBO) rather than the 60 mg dose. The Agency supported the 50% dose reduction to maintain adequate efficacy exposure comparable to the 60 mg dose while balancing the benefit-risk and efficacy-safety in patients with lower body weight, moderate renal impairment, and those using select P-gp inhibitors.
- Patients received study treatment for ≥ 3 months and ≤ 12 months, determined by the investigator based on the patient's clinical features.
- Patients were excluded if they required thrombectomy, insertion of a caval filter, or use of a fibrinolytic agent, had a CrCl < 30 mL/min, significant liver disease or active bleeding.

Demographics

Treatment groups were balanced across demographic and baseline characteristics: age (mean age ~ 56 years), gender (57% male), race (70% Caucasian, 21% Asian and 4% Black), baseline diagnosis and risk factors. The initial diagnosis was PE (with or without DVT) in 40.6% and 40.7% of edoxaban and warfarin patients, respectively, and the initial diagnosis was DVT in 59.4% and 59.3% of edoxaban and warfarin patients, respectively. A total of 9.4% of patients reported a past history of cancer, including 2.5% with active cancer at randomization.

At baseline, 27.5% of edoxaban and 27.7% of warfarin patients had only temporary risk factors (e.g., trauma, surgery, immobilization, estrogen therapy). Aspirin was taken as an on-treatment, concomitant anti-thrombotic medication by 9% of patients in the edoxaban and warfarin groups.

¹³ INR stands for the International Normalized Ratio, which is an internationally accepted scale used to measure prothrombin time. Prothrombin time (PT) measures how long it takes blood to clot. Normal lab values vary depending on which lab is doing the measurement, the INR gives providers a reference when evaluating a normal PT value.

Exposure in the Hokusai VTE Study ¹⁴

A total of 8,292 patients were randomized to receive edoxaban (60 mg) or warfarin, and 8,240 patients received study drug treatment. The mean treatment duration was 252 days for edoxaban and 250 days for warfarin. In the study drug treatment groups, 62.1% and 60.9% of patients received edoxaban and warfarin, respectively, and > 6 months of treatment (including 40.3% and 40.2% of patients who received 12 months of study treatment). In the warfarin group, the median time in therapeutic range (TTR), INR 2.0 to 3.0, was 65.6% with edoxaban.

Hokusai VTE Study, Primary Efficacy Results

The primary efficacy endpoint analysis was based on all primary efficacy events that occurred in the modified Intent-to-treat (mITT) population during the 12-month study period. The primary efficacy endpoint (Hokusai study) is symptomatic recurrent VTE (i.e., the composite of DVT, non-fatal PE, and fatal PE during the 12-month study) based on the Clinical Events Committee (CEC) adjudication. As shown in **Table 3**, edoxaban, 60 mg, is demonstrated to be non-inferior to warfarin for the primary efficacy endpoint of recurrent VTE (within a non-inferiority margin of 1.5), [HR (95% CI): 0.89 (0.70, 1.13)].

¹⁴ The combined exposure for edoxaban (Engage and Hokusai study) is 34,100 patient-years and for warfarin is ~ 18,300 patient-years. These two P-3 studies include 18,132 patients treated with edoxaban (7,002 with edoxaban 30 mg and 11,130 patients treated with edoxaban 60 mg) and 11,134 treated with warfarin. See the Clinical Review for Efficacy with Edoxaban, written by Melanie Blank, M.D., DCRP, for details on clinical efficacy in the Engage study (AF).

Table 3. Primary Composite Efficacy Endpoint Results in Hokusai VTE (mITT Study Period)

Primary Endpoint	Edoxaban ^a	Warfarin	Edoxaban vs Warfarin HR (95% CI)
All patients with symptomatic recurrent VTE ^b , n/N (%)	130 / 4,118 (3.2)	146 / 4,122 (3.5)	0.89 (0.70, 113)
PE with or without DVT	73 / 4,118 (1.8)	83 / 4,122 (2.0)	-
Fatal PE and Death where PE cannot be ruled-out	24 / 4,188 (0.6)	24 / 4,122 (0.6)	-
On-fatal PE	49 / 4,118 (1.2)	59 / 4,122 (1.4)	-
DVT only	57 / 4,118 (1.4)	63 / 4,122 (1.5)	-
All Patients with Index PE ^c , n/N (%)	47 / 1,650 (2.8)	65 / 1,669 (3.9)	-
Patients with Index DVT only, n/N (%)	83 / 2,468 (3.4)	81 / 2,453 (3.3)	-
Abbreviations: mITT-Modified intent-to-treatment; HR-Hazard Ratio vs warfarin; CI-confidence interval; N-number of patients in mITT population; n = number of events			
^a Includes patients dose-reduced to 30 mg;			
^b Primary Efficacy Endpoint: Symptomatic recurrent VTE (ie, the composite endpoint of DVT, non-fatal PE and fatal PE			

(b) (4)

For patients (n = 733) who received the 30 mg edoxaban dose-adjusted regimen, the efficacy (and safety) was comparable to patients who received edoxaban 60 mg dose. See the primary efficacy analysis (by edoxaban dose) in the Clinical Review by Saleh Ayache, MD, DHP.

The secondary efficacy endpoint is the composite clinical outcome of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, and all-cause mortality during the 12-month study. If non-inferiority is established for the primary efficacy endpoint, it is pre-specified that the secondary efficacy be tested for superiority at $\alpha=0.01$ (two-sided). The Hokusai study failed superiority on the secondary efficacy endpoint (see **Table 4**).

Table 4. Secondary Efficacy Analysis Results, Hokusai VTE Study

Secondary Efficacy Endpoint	Edoxaban; N = 4,118	Warfarin; N = 4,122
Patients with recurrent VTE or All-Cause Mortality, n (%)	228 (5.5%)	228 (5.5%)
Recurrent non-fatal VTE	106 (2.5)	122 (3.0)
All-Cause Mortality	122 (3.0)	106 (2.5)
VTE-related Death	24 (0.6)	24 (0.6)
Infectious Dis. related Death	25 (0.6)	12 (0.2)
Other Death	73 (1.8)	76 (1.8)
HR (95% CI)	1.00 (0.83, 1.20)	
p-value (for superiority)	0.99	

Table modified from Mid-Cycle slides by Saleh Ayache, MD, Clinical Reviewer, DHP.

Hokusai VTE Study, Primary Safety Endpoint Results

The primary safety endpoint was clinically relevant bleeding (CRB), defined as the composite of major or CRNM bleeding that occurred during treatment or within 3 days after stopping study treatment.

Major Bleed: overt bleeding with fall in Hgb of 2 g/dL; need for RBC transfusion of > 2 units; intracranial, intraspinal, intraocular, pericardial, intramuscular with compartment syndrome, intraarticular or retroperitoneal; death.

Clinically relevant non-major bleeding (CRNM): Epistaxis lasting > 5 minutes; gingival bleeding lasting > 5 minutes; macroscopic hematuria; macroscopic GI bleeding or rectal bleeding of > a few spots; hemoptysis of more than a few speckles; intramuscular hematoma or subcutaneous hematoma > 25 cm².

Other safety endpoints: Death; Special Interest Events; MACE defined as non-fatal myocardial infarction (MI); non-fatal stroke; and non-fatal systemic embolic events (SEE), and cardiovascular (CV) death); serious adverse events (SAEs); hepatotoxicity. Brief comments follow on major risks.

– Bleeding Events

Edoxaban is superior to warfarin for the primary safety endpoint of CRB, 8.5% of patients in the edoxaban group and 10.3% of patients in the warfarin group [HR (95% CI): 0.81 (0.71 to 0.94); p = 0.004 for superiority]. See the Kaplan-Meier Cumulative Event Rate Estimate for the Primary Safety Endpoint (Adjudicated Major/CRNM Bleeding).¹⁵ Edoxaban demonstrated a sustained relative risk reduction (RRR) in major/CRNM bleeding up to 12 months.

Compared with warfarin, edoxaban had numerically lower incidences of major bleeding events (1.4% for edoxaban vs. 1.6% for warfarin), fatal bleeding [2 edoxaban vs. 10 warfarin], fatal and non-fatal intracranial bleeding (0 edoxaban vs. 6 warfarin), critical

¹⁵ NDA 206-316 Edoxaban, GS, Module 2, Subsection 2.5 Clinical Overview, Figure 5.1, page 42. The Kaplan-Meier plot (with DHP edits) appears in the proposed labeling for edoxaban.

site bleeding (13 edoxaban vs. 32 warfarin), nuisance bleeding (16.1% vs. 19.1%), and any bleeding (21.7% vs. 25.6% for warfarin).

Among the patients (n = 733) who received the reduced 30 mg dose of edoxaban, 58% experienced a major bleeding or CRNM event.

– **Gastrointestinal Tract and Vaginal Bleeding Events**

Major bleeding was lower for edoxaban in most anatomic sites but not in the GI tract or with vaginal bleeding with the 60 mg dose. Numerical imbalances in GI tract and vaginal bleeding events were reported with edoxaban vs. warfarin treatment: 27 (0.7%) vs. 18 (0.4%), respectively. This difference in GI tract bleeding was less pronounced with Major/CRNM bleeding (2.4% edoxaban vs. 2.3% warfarin treatment). Numerically more vaginal bleeding events are reported with edoxaban vs. warfarin for both Major bleeding [9 (0.5%) vs. 3 (0.2%)] and Major/CRNM bleeding [81 (4.6%) vs. 56 (3.2%)].¹⁶

– **Major Adverse Cardiovascular Events**

Employing the composite endpoint, MACE, edoxaban demonstrated 1.2% events vs. warfarin 1% events. This higher incidence of MACE with edoxaban vs. warfarin is causally attributed to a higher incidence of reported MI events (20 [0.5%] for edoxaban vs. 13 [0.3%] for warfarin). The relative risk reduction (RRR) in Major/CRNM bleeding with edoxaban treatment was sustained up to 12 months.

– **30 mg Edoxaban Dose Adjusted Regimen and Bleeding Events**

In patients treated with the reduced edoxaban 30 mg dose, bleeding rates were comparable to those with edoxaban 60 mg dose. The sensitivity analyses are consistent with the primary safety results. In the edoxaban and warfarin treatment groups, 62.1% and 60.9% of patients, respectively, received at least 6 months of treatment, and, 40.3% and 40.2% of patients, respectively, received 12 months of treatment.

– **VTE Recurrence Rate on Edoxaban compared with Warfarin**

Though the applicant submitted clinical data on the rate of recurrence of VTE based on the Hokusai study, this study protocol was not designed to evaluate and analyze recurrent VTE data. As cited earlier in this review, these data may be considered as proof-of-concept and appear to demonstrate that, beyond the first 30 days, patients who continued on edoxaban treatment > 12 months experienced lower rates of VTE recurrence compared with patients on warfarin treatment.

– **Supportive Efficacy Results**

Advanced age and cancer are associated with early mortality after VTE. In subgroup analyses of fragile patients, elderly patients and patients with cancer, edoxaban demonstrates a favorable outcome compared with warfarin. See the Clinical Review written by Saleh Ayache, MD, DHP, for detail on these results.

3.1 Clinical Safety - Hokusai Study

¹⁶ NDA 206-316, Edoxaban, GS. Module 2.7.4 Clinical Safety, (Hokusai Study), pp 106-107.

In the Hokusai study, clinical safety data for edoxaban includes 4,118 patients treated with edoxaban 60 mg and 4,122 patients treated with warfarin.

Discontinuations

The patients who discontinued study treatment (edoxaban, 16.9%, or warfarin, 17.4%) were comparable across the two treatment groups. An adverse event (AE) was the most common reason for a patient to stop study participation, [233 (5.7%) of edoxaban patients and 222 (5.4%) of warfarin patients].¹⁷ More patients discontinued from the 30 mg edoxaban treatment compared with the 60 mg edoxaban treatment, [26.3% (30 mg) compared with 14.8% (60 mg) for active edoxaban patients vs. 24.3% (30 mg) compared with 16% (60 mg) for active warfarin patients].¹⁸

The serious adverse events (SAEs) that prompted permanent discontinuation are comparable across treatment groups: 4.7% vs. 4.5%, edoxaban vs. warfarin, respectively.¹⁹

- Hepatic enzyme elevations elevated in 10 edoxaban-treated patients vs. 8 warfarin-treated patients, sepsis (4 vs. 0), dyspnea (3 vs. 0), nausea (3 vs. 0), and renal failure acute (3 vs. 0), edoxaban vs. warfarin, respectively.
- In contrast, the INR increased (0 vs. 13) and renal impairment (2 vs. 4) were reported more with warfarin vs. edoxaban treatment, causing discontinuation of treatment.²⁰

Common Adverse Reactions

- The most common adverse reactions ($\geq 1\%$) related to bleeding with edoxaban 60 mg vs. warfarin were: vaginal hemorrhage (9.0% vs 7.1%), cutaneous soft tissue hemorrhage (5.9% vs. 10%), epistaxis (4.7% vs. 5.7%), oral/pharyngeal hemorrhage (3.4% vs. 3.9%), lower GI hemorrhage (3.4% vs. 3.1%), macroscopic hematuria/urethral (2.2% vs. 2.8%), and puncture site hemorrhage (1.4% vs. 2.4%), respectively.
- The most common non-bleeding adverse reactions ($\geq 1\%$) were: rash, abnormal liver function tests, and anemia.

Serious Adverse Reactions

¹⁷ The protocol violations were small, 22 events (0.5%) with edoxaban and 22 events, (0.5%) with warfarin.

¹⁸ NDA 206-316, Edoxaban, GS, Module 2.0, Subsection 2.5 Clinical Safety, p 127.

¹⁹ In the edoxaban treatment group, the most frequent SAE by SOC that caused permanent discontinuation were: Neoplasm Benign, Malignant and Unspecified SOC (1%), Investigations SOC (0.6%), followed by Infections and Infestations SOC and Gastrointestinal Disorders SOC (0.4%, each), and Cardiac Disorders, Respiratory, Thoracic and Mediastinal Disorders, and Skin and Subcutaneous Tissue Disorders SOCs (0.3%, each). In the warfarin treatment group, the most frequent SAE by SOC that caused permanent discontinuation were: Neoplasm Benign, Malignant and Unspecified SOC (0.9%) followed by Investigations SOC (0.8%).

²⁰ NDA 206-316 Edoxaban, GS, Module 2.7.4 Summary of Clinical Safety, p 124-125.

- The most frequent SAEs, reported by system organ class (SOC) in the edoxaban treatment group were: Infections and Infestations SOC (2.6%); Neoplasm Benign, Malignant and Unspecified SOC (1.9%); Respiratory, Thoracic and Mediastinal Disorders (1.4%); Injury, Poisoning and Procedural Complications (1.2%); and Cardiac Disorders (1.1%). The Preferred Term (PT) of anemia is reported in 3 (<0.1%) edoxaban-treated patients and 10 (0.2%) warfarin-treated patients.
- The most frequent SAEs, reported by SOC in the warfarin treatment group were: Neoplasm Benign, Malignant and Unspecified SOC (2.4%); Investigations SOC (2.1%); Infections and Infestations SOC (2.0%); Injury, Poisoning and Procedural Complications (1.4%); and Respiratory, Thoracic and Mediastinal Disorders (1.3%).²¹
- The SAEs reported in the Investigations SOC were comparable with the exception of more Investigation events (INR increased for the warfarin treatment group).

Deaths

In the Hokusai study, the all-cause mortality is comparable across the edoxaban treatment group (35 deaths, 0.8%) and warfarin treatment group (33 deaths, 0.8%) as shown in **Table 5**. There are 6 CV deaths reported with edoxaban vs 3 CV deaths reported with warfarin; 2 deaths with edoxaban causally attributed to ischemic stroke vs none with warfarin. The category of Other Cardiac Death is reported in 3 patients with edoxaban vs. 1 patient with warfarin. There was an excess of non-VTE related deaths, specifically, infectious disease mortality (25, 0.6%) with edoxaban treatment vs. (12, 0.3%) with warfarin treatment.

Table 5. Primary Cause of Death (Safety Analyses, On Treatment-Hokusai Study)

Cause of Death	Edoxaban (N = 4118), n (%)	Warfarin (N = 4122), n (%)
All Causes	35 (0.8)	33 (0.8)
VTE-Related Death	13 (0.3)	10 (0.2)
- PE	2 (<0.1)	0 (0.0)
- Unexplained Death (and VTE cannot be ruled out)	11 (0.3)	10 (0.2)
Cardiovascular Death	6 (0.1)	3 (<0.1)
MI	1 (<0.1)	2 (< 0.1)
Ischemic stroke	2 (<0.1)	0 (0)
SEE	0 (0)	0 (0)
Other Cardiac Death ^a	3 (<0.1)	1 (< 0.1)
Other Known Cause	16 (0.4)	20 (0.50)

Taken from NDA 206-316, Edoxaban, GS, Module 2, Subsection 2.7.4 Clinical Safety, Table C-2.9, p 119

The imbalance in deaths appears to be causally attributed to infectious disease events in the controlled study period (0.6% vs 0.3%). All-cause mortality (across combined studies) was numerically lower and cardiovascular mortality was lower for edoxaban-treated patients compared with warfarin-treated patients.

²¹ NDA 206-316, Edoxaban, GS, Module 2.7.4 Summary of Clinical Safety, p 122-123

Adverse Events of Special Interest

Hepatotoxicity

In the Hokusai study, no hepatic Hy's law cases were confirmed in patients exposed to edoxaban.²² However, there were numerous reported cases with increased hepatic enzymes as alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≥ 8 x upper limit of normal (ULN) observed in patients exposed to edoxaban and warfarin. Per John R. Senior, MD, Hepatology Consultant (dated August 8, 2014), there were no events of Hy's Law cases of drug-induced hepatocellular jaundice with edoxaban or warfarin in the Hokusai VTE study (or the Engage AF study) despite numerous patients with liver enzyme abnormalities [Hokusai study: 285 patients (6.9%) edoxaban treatment vs. 288 patients (7%) warfarin treatment]. Among these liver enzyme abnormalities, edoxaban vs. warfarin, 5.2% vs. 5.5% are considered mild; 1.4% vs. 1.5% are considered moderate; and 4 cases (<0.1%) vs. 6 cases (<0.1%) considered severe, respectively.²³ Currently, hepatotoxicity does not appear in the Warnings and Precautions section of the proposed edoxaban labeling (per DHP). Labeling revisions, per the DCRP, are pending.

Malignancy

Patients treated with anticoagulant therapy may be diagnosed with cancer following a bleeding event and a VTE may be a presenting sign when diagnosing a patient who has an underlying malignancy. The number of malignancies newly diagnosed, relapsed or progressed among edoxaban treated patients was 117 (2.8%) vs. 137 (3.3%) among the warfarin treated patients. As of this review, malignancy does not appear in the Warnings and Precautions (Section 5) of proposed edoxaban labeling. Labeling revisions, per the DCRP, are pending.

Risk of Bleeding

As cited earlier in **Section 3**, of this review, the primary safety endpoint (Hokusai study) is major or CRNM bleeding and is reported in 58 patients (7.9%). Edoxaban, as with other oral anti-coagulants, is associated with the risk of bleeding and can cause serious and potentially fatal bleeding based on its mechanism of action as a FXa inhibitor. Per the clinical pharmacology reviewer, the anticoagulant effect of edoxaban may persist for

²² Hepatology Consult by John R. Senior, MD, Associate Director of Science, OPE (dated August 8, 2014) As cited by John R. Senior, Dr. Robert Temple coined the term, Hy's Law, in 1999 (serum enzymes are not indicative of liver function. Impaired clearance of bilirubin or impairment of prothrombin synthesis are signs of impaired liver function. Dr. Hyman Zimmerman observed that drug-induced hepatocellular injury with jaundice is a grave illness with estimated mortality of 10 -50%. Hy's Law –ALT > 3 X ULN + total bilirubin 2 x ULN. This Law is most helpful when evaluating specificity of ALT testing in clinical trials.

²³ Per John R. Senior, M.D., although there were fairly frequent serum ALT elevations, there were no notable differences between the incidences of edoxaban- and warfarin-treated patients. The incidence of potentially more serious liver injury with whole-organ dysfunction, as shown by serum bilirubin elevations, was very low: 11/4,122 patients (0.27%) or 1/375 patients treated with edoxaban and 6/4,118 patients (0.15%) or 1/686 patients treated with warfarin. When cases with both ALT and total bilirubin (TBL) elevations above 3 x ULN and 2 x ULN, respectively, were evaluated using the evaluation of **Drug-Induced Serious Hepatotoxicity (eDISH)** program to assess the time-course of all liver tests [ALT, TBL, AST and alkaline phosphatase (ALP)] over the entire period of observation..., there were no cases found of probable Hy's Law cases of drug-induced hepatocellular jaundice, from either drug treatment.

~ 24 hours after the last dose (2 half-lives).²⁴ The risk of bleeding appears in the Warnings and Precautions (Section 5) of the proposed edoxaban labeling (per DHP edits).

120-Day Safety Update Report

The safety data with edoxaban proposed for the treatment of DVT and PE are consistent with the safety profile reported in the original NDA. See the **Appendix**, to this review, **Brief Summary of Results: 120-Day SUR**. See the Clinical Review by Saleh Ayache, MD, DHP for details on the 120-Day SUR.

4 DISCUSSION

Hokusai VTE Study

In the Hokusai VTE study, edoxaban 60 mg, once daily, was non-inferior to warfarin for the primary efficacy endpoint of recurrent VTE (within a non-inferiority margin of 1.5), [HR (95% CI): 0.89 (0.70, 1.13)]. The secondary efficacy endpoint is the composite clinical outcome of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, and all-cause mortality during the 12-month study. The Hokusai study failed to achieve superiority to warfarin on the secondary efficacy endpoint.

The primary safety endpoint was achieved with edoxaban demonstrating superiority ($p < 0.005$) with a RRR of 19% and an absolute RR (ARR) of 1.8% across bleeding categories. Patients treated with edoxaban had numerically less fatal bleeding, less fatal and non-fatal ICH bleeding, and less critical site bleeding compared to warfarin. The RRR for edoxaban in Major/CRNM bleeding events was sustained up to 12 months of treatment. The edoxaban reduced 30 mg dose (proposed for patients with lower body weight, impaired renal function, and concomitant use of P-gp inhibitors) demonstrated comparable efficacy to patients treated with 60 mg edoxaban.

The exposure-response data demonstrated that edoxaban 60 mg, once daily, provides optimal systemic exposure. The safety data demonstrated no adverse, significant exposure-response relationship between clinically relevant bleeding within the exposure range achieved with 60 mg and 30 mg doses. The bleeding rates with edoxaban, 30 mg, were comparable to the 60 mg dose.



²⁴ See revised draft edoxaban labeling, Warnings and Precautions, Section 5.2 Risk of Bleeding

Serious Risk of Bleeding

The principal serious safety risk reported with edoxaban is the risk of major bleeding. The safety profile of edoxaban, 60 mg, in regard to the risk of major bleeding, is consistent with the class of NOAC drug product with the exception of a higher frequency of GI tract bleeding and vaginal bleeding compared with the active control, warfarin (Hokusai VTE study).

The class of NOAC drug products and warfarin are the current medical treatment-of-choice for patients with thrombotic events. The class of NOAC drug products is associated with the serious risk of bleeding events and of thromboembolic events, the latter a serious risk in patients with non-valvular AF.

Labeling for each of the approved NOAC drug products as well as for ticagrelor include the serious risk of bleeding in the Warnings and Precautions section. The risk of bleeding events, Major/CRNM bleeding, is less with edoxaban compared to warfarin, with the exception GI major bleeding events and vaginal bleeding events in which there are reported imbalances with edoxaban compared to warfarin (Hokusai study).

The etiology of the risk of increased gastrointestinal bleeding and vaginal bleeding with edoxaban remains unclear. Postmarketing pharmacovigilance data, if edoxaban is approved, will support characterization of the risks of GI tract and vaginal bleeding observed with edoxaban in the Hokusai study. At this time, the DHP and the DRISK do not recommend requirement of a REMS for edoxaban for the proposed treatment of DVT and of PE. The risk of bleeding will appear in the Warnings and Precautions section of proposed labeling and will include the need for careful clinical monitoring by prescribers during and after edoxaban therapy.

Savaysa (edoxaban), if approved, will be the fourth-in-class NOAC drug product (approved NOAC drug products are rivaroxaban, apixaban and dabigatran). The major safety concern with the NOAC drug products is the risk of bleeding. Based on clinical experience with the NOAC drug products and with ticagrelor (a P2Y12 platelet inhibitor), prescribers most likely to prescribe edoxaban are familiar with the reported safety risks with the NOAC drug products as well as with ticagrelor. Each of these five products (cited above) were required to have a REMS for approval.

Rivaroxaban and dabigatran are approved for treatment of DVT and PE; apixaban is approved for prophylaxis of DVT which may lead to PE. Ticagrelor (Brilinta), approved for a different indication, to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome, is the only product (among those cited above) in which the REMS goals included the major risk of bleeding. The Brilinta REMS requirement was released on October 30, 2013 based on acceptable REMS assessments. The Brilinta REMS assessments demonstrated that providers understand the safety risks associated with this drug product.

The REMS requirement for Xarelto (rivaroxaban) and Pradaxa (dabigatran) were both released on February 14, 2014 and April 5, 2014, respectively. The decisions to release these product REMS were based on post marketing safety and acceptable REMS assessment reports. The REMS assessment reports demonstrated that the goals of these REMS have been adequately achieved and that there is acceptable provider

understanding of the known serious risks associated with use of each drug product. The REMS for Eliquis (apixaban) is ongoing with dissemination of educational materials under the communication plan.

The Agency continues to monitor the risk of GI bleeding in these agents. The Agency completed a new study in Medicare patients (> 134,000 Medicare patients, 65 years or older) comparing Pradaxa to warfarin, for the risk of ischemic or clot-related stroke, bleeding in the brain, major GI bleeding, MI, and death. The findings of an increased risk of major GI bleeding with use of Pradaxa as compared to warfarin prompted the Agency to issue a Drug Safety Communication (dated May 19, 2014) entitled, “Pradaxa (dabigatran) - FDA Drug Safety Communication: Lower Risk Stroke and Death, but Higher Risk for GI Bleeding Compared to Warfarin.” The target audience cited in this safety communication includes cardiology, pulmonary, Internal Medicine, Orthopedics, Neurology and patients.

Anti-Coagulant Effect of Edoxaban

The anticoagulant effect of edoxaban cannot be reliably monitored with standard laboratory testing and there is, currently, there is no available product to reverse the anti-FXa activity of edoxaban, or other NOAC drug products, or warfarin. Rivaroxaban, apixaban and dabigatran do not require periodic laboratory testing of a patient’s clinical response, in contrast to the necessary laboratory monitoring with warfarin therapy.

Hepatotoxicity

Hepatotoxicity is a known safety risk with the rivaroxaban (a FXa inhibitor) and with ticagrelor (a P2Y₁₂ platelet inhibitor) in patients with hepatic impairment. Hepatic adverse events are reported with edoxaban in the Hokusai VTE study and the Engage non-valvular AF study. As reported by John R. Senior, Hepatology Consultant, no cases of Hy’s Law were confirmed in NDA 206-316 for edoxaban despite numerous patients with elevated liver enzymes with and/or without increases in serum total bilirubin.

As of this review, the proposed edoxaban labeling (per the DHP) does not include the risk of hepatotoxicity in the Warnings and Precautions section. Currently, no edoxaban dose reduction is recommended in patients with mild (b) (4) hepatic impairment. As of this review, no studies with edoxaban have been conducted in patients with severe hepatic impairment.

Switching NOAC Treatment

Withdrawal of an anti-coagulant drug product results in a prothrombotic state. Inadequate coagulation and the subsequent risk of developing a DVT and/or PE, or a stroke, is a known safety risk when transitioning a patient from one FXa inhibitor (i.e., rivaroxaban, apixaban) to another FXa inhibitor, or to warfarin. At this time, the proposed edoxaban labeling recommendations for switching anticoagulant therapy are being revised by DHP (and DCRP).

Patient information

Patient safety information on edoxaban will be provided as a Medication Guide, as part of labeling, if edoxaban is approved.

As noted in the **Introduction** of this review, the applicant did not submit a RMP for edoxaban or propose a REMS. As stated earlier in this **Section 4 Discussion**, edoxaban will be the fourth-in-class NOAC drug product, if approved. The safety profile of the three approved NOAC drug products is well characterized.

This reviewer concurs with the DHP that edoxaban, based on clinical efficacy and safety data in NDA 206-316, demonstrates a safety profile consistent with the approved NOAC drug products. This reviewer concurs with the DHP that the reported serious risks associated with use of edoxaban may be managed via routine labeling, to include a Medication Guide, and via a routine pharmacovigilance plan. This reviewer does not recommend a REMS for edoxaban (proposed for the treatment of DVT and of PE) to ensure that the benefits of this drug outweigh the risks.

At this time, the proposed edoxaban labeling, Warnings and Precautions (Section 5), includes the following:

- (b) (4) Increased Risk of Stroke with Discontinuation of Edoxaban in Patients with Non-valvular Atrial Fibrillation
- (b) (4) Risk of Bleeding
- (b) (4) Spinal/Epidural Anesthesia or Puncture (will include recommendations on timing for removal of an indwelling catheter or intrathecal catheter after the last administered dose of edoxaban, if approved)
- (b) (4) Patients with Mechanical Heart Valves

Each of the three NOAC drug products and Brilinta (ticagrelor) have a Medication Guide in the approved drug product labeling. There are no new serious risks reported with edoxaban in the 120-Day SUR to NDA 206-316. At this time, each of the approved NOAC drug products is monitored via a routine pharmacovigilance plan.

The target audience for the proposed edoxaban indication (treatment of DVT and PE) appears to be the same audience that the Agency targeted for the FDA Drug Safety Communication on Pradaxa (dabigatran), “Lower Risk for Stroke and Death, but Higher Risk for GI Bleeding Compared to Warfarin,” specifically, cardiology, patients, pulmonary, Internal Medicine, Orthopedics and Neurology. Based on three NOAC drug product REMS assessment report provider survey results of knowledge assessment, the physicians most likely to prescribe edoxaban, if approved, are familiar with the known serious risks associated with use of a NOAC drug product as well as warfarin.

A separate DRISK analysis and review will be provided by Cathy Miller, MPH, BSN,, that addresses the findings and risk management considerations for edoxaban proposed to reduce the risk of stroke and SE in patients with non-valvular AF (in the DCRP).

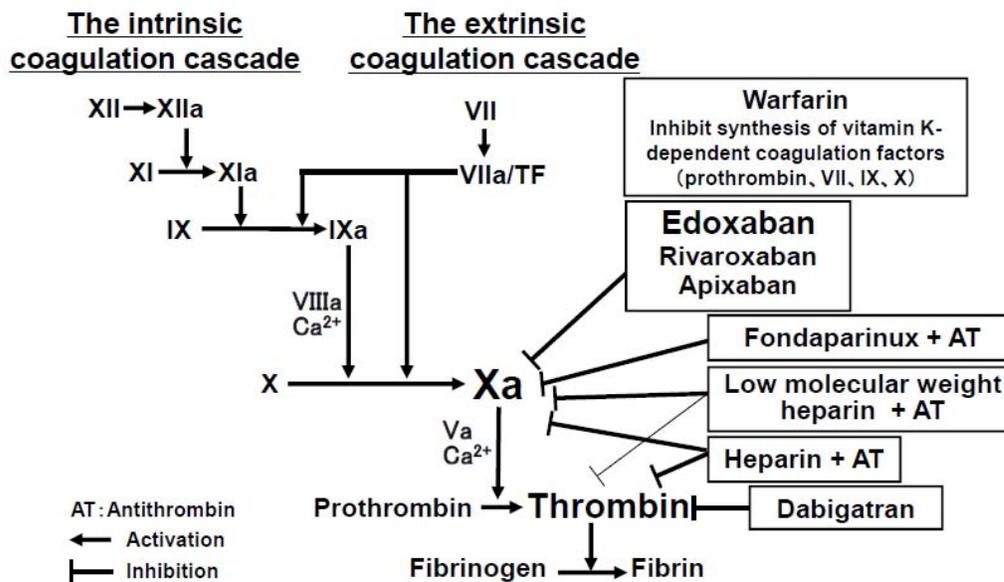
5 CONCLUSION

The DRISK and the DHP concur that a REMS is not required for edoxaban to ensure that the benefits outweigh the risks for the proposed treatment of patients with DVT and PE who have been treated with a parenteral anticoagulant for 5 to 10 days (in the DHP). Based on the totality of the clinical efficacy and safety data, this reviewer does not recommend a REMS, at this time, to ensure that the benefits of edoxaban (proposed for

the treatment of DVT and of PE) outweigh the risks. The DHP should consult the DRISK if additional safety information is identified that warrants re-evaluation of the risk management measures for edoxaban oral tablets.

APPENDIX

Figure 1. Blood Coagulation Cascade and Sites of Action of Anticoagulants



Revised from the NDA 206-316, Edoxaban, GS, Module 2.6, Non-Clinical Written Summary, page 46

Table 1. Acquired Causes of Venous Thrombosis

Significant Risks:
Surgery
Neurosurgery
Major abdominal surgery
Major orthopedic surgery
Moderate Risks:
Malignancy
Cancer
Anti-phospholipid syndrome
Other Risks:
Trauma
Pregnancy
Long-distance travel (air travel > 4 hrs)
Obesity
Prolonged bed-rest
Oral contraceptives/hormone replacement
Myeloproliferative disorders
Polycythemia vera
Table revised from Table 117-3. Acquired Causes of Venous Thrombosis. Chapter 117, Arterial and Venous Thrombosis by J. E. Freedman, J Loscalzo. Harrison's Principles of Internal Medicine, 18 th Ed., Vol 1, p 987.

Table 2. NOAC Products - Oral Tablets. See the next page.

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Table 2. Novel Oral Anticoagulants (NOACs) Products and One P2Y12 Platelet Inhibitor					
Product/Brand	Edoxaban / SAVAYSA	Rivaroxaban / XARELTO	Apixaban / ELIQUIS	Dabigatran / PRADAXA	Ticagrelor / BRILINTA
BLA / NDA	NDA 206-316	NDA 022-406	NDA 202-155	NDA 022-512	NDA 022-433
Approval Date	<i>PDUFA Date: 08Jan2015</i>	1-Jul-11	28-Dec-12	19-Oct-10	20-Jul-11
Class	Reversible Factor Xa Inhibitor	Selective Factor Xa Inhibitor	Factor Xa Inhibitor	Direct Thrombin Inhibitor	P2Y12 Platelet Inhibitor
Indication	<p><i>Proposed:</i> To reduce the risk of stroke, systemic embolism (SEE) in pts w nonvalvular AF;</p> <p>Tx of DVT: (b) (4)</p> <p>Tx of PE (b) (4)</p> <p>for DVT and/or PE</p>	<p>To reduce the risk of stroke and SEE in pts w non-valvular AF; Treatment of DVT, PE, and reduction in risk of recurrence of DVT and of PE;</p> <p>For prophylaxis of DVT, which may lead to PE in pts undergoing knee or hip replacement surgery</p>	<p>To reduce the risk of stroke and SEE in pts w non-valvular AF; For prophylaxis of DVT, which may lead to PE, in pts post hip or knee replacement surgery</p>	<p>To reduce risk of stroke and SEE in pts. w non-valvular AF; Treatment of DVT and PE; Reduction in risk of recurrence of DVT/PE</p>	<p>To reduce rate of thrombotic CV events in pts with acute coronary syndrome (ACS)</p>
Boxed Warning	None Proposed	Yes	Yes	Yes	Yes
Contra-indications	Active pathological bleeding	Active pathological bleeding; Severe hypersensitivity reaction to XARELTO	Active pathological bleeding; Severe hypersensitivity reaction to ELIQUIS	Active pathological bleeding; Hx of serious hypersensitivity; Mechanical prosthetic heart valve	Hx of ICH; Active pathological bleeding; Severe hepatic impairment; hypersensitivity to BRILINTA
Warnings & Precautions	Risk of Bleeding; Pts w Mechanical Heart Valves; Increased Risk of Thrombotic Events after Premature D/C	<p>Increased Risk of Thrombotic Events after Premature D/C;</p> <p>Risk of Bleeding;</p> <p>Spinal/Epidural Anesthesia or Puncture;</p> <p>Use in Pts w Renal Impairment;</p> <p>Use in Pts w Hepatic Impairment;</p> <p>Use w P-gp and Strong CYP3A4 Inhibitors or Inducers;</p> <p>Risk of Pregnancy-Related Hemorrhage;</p> <p>Pts w Prosthetic Valves;</p> <p>Acute PE in Hemodynamically Unstable Pts or Pts Who Require Thrombolysis or Pulm Embolectomy</p>	<p>Increased Risk of Stroke w Discontinuation of ELIQUIS in Pts w Nonvalvular AF;</p> <p>Bleeding;</p> <p>Spinal/Epidural Anesthesia or Puncture;</p> <p>Pts w Prosthetic Heart Valves</p>	<p>Bleeding: PRADAXA can cause serious and fatal bleeding;</p> <p>Bioprosthetic heart valve: PRADAXA use not recommended.</p>	<p>General Risk of Bleeding;</p> <p>Concomitant ASA Maintenance Dose;</p> <p>Moderate Hepatic Impairment;</p> <p>Dyspnea;</p> <p>Discontinuation of BRILINTA;</p> <p>Strong inhibitors of Cytochrome CYP3A;</p> <p>Cytochrome CYP3A Potent Inducers;</p>
Medication Guide	<i>To be required per FDA</i>	Yes	Yes	Yes	Yes

REMS	<i>None Proposed</i>	REMS with a CP	REMS with CP	REMS with Medication Guide	REMS with CP
REMS Released	<i>N. A.</i>	REMS released, 12Feb2014	Last REMS Assessment, Jun2014; REMS is ongoing	REMS released, 05Apr2014	REMS released, 30Oct2013
Abbreviations: AF-atrial fibrillation; CP-communication plan; D/C-discontinuation; DVT-deep vein thrombosis; Hx-history; ICH-intracranial hemorrhage; N.A.-not applicable; P-gp: P-glycoprotein; w-with; Recomm-recommended; Pts-patients; Tx-treatment. EDOXABAN (LIXANA) approved in Japan July 2011 for prevention of DVT in patients who are post-op, lower limb orthopedic surgery.					

Brief Summary of Results: 120-Day SUR for Edoxaban

- There is a higher percentage of patients in the 120-Day SUR that are ≥ 75 years of age (10.7%) vs. 3.6% in the controlled data and patients of Black racial background (19.6%) vs. 7.1% in the controlled data.
- Adjudicated Major and CRNM bleeding events were comparable between the treatment groups (1/56 [1.8%] of patients, edoxaban-treatment group, and 1/28 [3.6%] patients, LMWH/warfarin-treatment group).
- There were two (2) additional deaths and both were adjudicated by the clinical events committee: one (1) patient in the warfarin treatment group experienced a fatal subdural hematoma (P-2, study DU211) and 1 patient in the edoxaban treatment group experienced a fatal hemorrhagic stroke.
- A total of 23 patients experienced SAEs in the P-2, D-U211, a proof-of-concept study with edoxaban 90 mg.
- A total of 20 patients experienced SAEs in the P-2 study E-U210, edoxaban 60 mg once daily plus aspirin (100 mg QD) for 3 months.
- A total of 21 pregnancies reported (18 with fetal exposure to study drug: 10 edoxaban vs. 8 warfarin) and 3 pregnancy cases reported off-study drug. A total of 4 live births (3 edoxaban vs. 1 warfarin) are reported and no congenital abnormalities are reported

See the Clinical Review for Edoxaban by Saleh Ayache, MD, DHP, for details on the 120-Day SUR.

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/s/

CAROLYN L YANCEY

09/17/2014

REMS Review for Edoxaban (in VTE in the DHP), NDA 206-316/ORIG-2 (b) (4)

CYNTHIA L LACIVITA

09/17/2014

Concur