CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206316Orig1Orig2s000

SUMMARY REVIEW

Summary Review for Regulatory Action

Date	(electronic stamp)
From	Ann. T. Farrell, M.D., Division Director
Subject	Division Director Summary Review
NDA/BLA # Supplement #	206316
Applicant Name	Daiichi Sankyo
Date of Submission	January 8, 2014
PDUFA Goal Date	January 8, 2015
Proprietary Name / Established (USAN) Name	SAVAYSA/edoxaban
Dosage Forms / Strength	15 mg, 30 mg and 60 mg tablets (immediate release)
Proposed Indication(s) for DHP	Orig 2- for the treatment of deep vein thrombosis (DVT) and for the treatment of pulmonary embolism (PE) (b) (4)
Action/Recommended Action for NME:	**Approval for a revised orig-2 indication** (b) (4)

Material Reviewed/Consulted OND Action Package, including:	
Medical Officer Review	Saleh Ayache, M.D./ Kathy Robie-Suh, M.D. Ph.D.
Statistical Review	Yun Wang, Ph.D./Lei Nie, Ph.D.
Pharmacology Toxicology Review	Baichun Yang, Ph.D./Tomas Papoian, Ph.D./Shwu Luan Lee, Ph.D./Haleh Saber, Ph.D./Paul Brown, Ph.D.
CMC Review/OBP Review	Akm Khairuzzaman, Ph.D., Debasis Ghosh, Ph.D., Yubing Tang, Ph.D., Sharmista Chatterjee, Ph.D., Olen M Stephens, Ph.D./Sandra Suarez Sharp, Ph.D./Angelica Dorantes, Ph.D.
Microbiology Review	Steven P. Donald/Stephen E. Langillle
Clinical Pharmacology Review	Young Jin Moon, Ph.D./Julie Bullock, Pharm.D. Divya Menon-Andersen, Ph.D., Justin Earp,Ph.D., Jeffry Florian, Ph.D.
OSI	Anthony Orencia, M.D., F.A.C.P./Janice Pohlman, M.D., M.P.H./Kassa Ayalew, M.D., M.P.H.
CDTL Review	Kathy Robie-Suh, M.D. Ph.D.
OSE/DMEPA	Denise V. Baugh, PharmD, BCPS/Tingting Gao, PharmD
OSE	John Senior, M.D./Carolyn Yancey, M.D., Doris Auth, Pharm.D., Cynthia LaCivita, Pharm.D.

Signatory Authority Review Template

1. Introduction

This NDA submission 206316 for SAVAYSA (edoxaban tosylate) a direct Factor Xa inhibitor proposed for [redacted] (b) (4):

1) for the reduction in the risk of stroke in patients with atrial fibrillation (Afib) – under review in the Division of Cardiovascular and Renal Products.
2) for treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) [redacted] (b) (4)

The PDUFA goal date is January 8, 2015.

2. Background

There are multiple products administered orally or intravenously approved to treat DVT and PE. The list includes warfarin, rivaroxaban, apixaban, dabigatran, warfarin, heparin, dalteparin, enoxaparin, and fondaparinux.

There are several products approved to prevent the recurrence of DVT and/or PE after the initial treatment. This list includes: rivaroxaban, apixaban, dabigatran, warfarin, heparin, and dalteparin. Note that for all approved products to prevent recurrence (after an initial VTE) adequate and well-controlled trials with acceptable statistical analysis plans have been conducted.

3. CMC/Device

There are no issues which would preclude approval.

The CMC review noted that:
Proposed shelf life is 36 months at long term storage conditions of

25ºC/60%RH. This is supported by 24 months of registration stability batch data and 48 months of clinical (phase 3) batch stability data. Batches used in the registration stability program were manufactured by the final commercial process at pilot-scale.

From the Biopharmaceutics Review there are two post-marketing commitments:
In a teleconference dated Sep 4, 2014 and in a submission dated Sep 05, 2104, the Applicant
agreed to have a Post-Marketing Commitment to be fulfilled within 15 months from action date for: i) development of a new dissolution method, which shows greater discriminating ability and follows the typical behavior when implementing changes to the critical quality attributes, and ii) setting of the final dissolution acceptance criterion of their drug product using the new method and the overall dissolution profile data from a minimum of 12 commercial batches.

4. Nonclinical Pharmacology/Toxicology

No issues that would preclude approval were identified. The following text is taken from Dr. Yung's primary review:

The nonclinical profile of DU-176b and its main human specific metabolite D21-2393 were investigated in a series of pharmacological, pharmacokinetic, and toxicological studies. Findings from pivotal toxicological studies included (I) increased polyploidy in chromosomal aberration tests; (II) hemorrhage in mice, rats, rabbits, and monkeys; (III) more post-implantation loss, less live fetuses, lower fetal weight, increased gall bladder and skeletal variations, and delayed avoidance response in a learning test in F1 females, which were associated with maternal hemorrhagic toxicity; and (IV) higher mortality in male rats at the high dose in a 2-year carcinogenicity study that was associated with higher incidence and greater severity of centrilobular hepatocellular degeneration/ necrosis.

The following text is taken from Dr. Lee's primary review:

Edoxaban (DU-176b) is an anti-coagulant exerting its pharmacodynamics effects mainly via inhibition of activated coagulation factor X (Factor Xa; FXa). Edoxaban also had inhibitory activity against thrombin. The Ki for FXa was ~0.6 nM and for thrombin was 6 μM, indicating less inhibition toward thrombin. Edoxaban demonstrated comparable FXa inhibition in human, rabbit, and cynomolgus plasma (Ki values ~0.5-0.7 nM), while less inhibition was observed in rat plasma. When two mutant forms of factor Xa were used in the assays, edoxaban exhibited comparable anticoagulation activity toward the wild-type or the mutants.

The three metabolites of edoxaban (D21-1402-0201, D21-2135-0101, D21-2393) also had anti-FXa activity and caused clotting time prolongation. Among these active

metabolites, the human specific metabolite D21-2393 (10% of the total exposure in healthy human subjects) showed comparable anti-coagulant effects as edoxaban. In various animal models, oral administration of edoxaban resulted in dose-dependent anti-thrombotic activity, as manifested by reduced weight of thrombi, as well as prolongation of clotting time. Under the conditions tested, the antithrombotic effects, in terms of PT prolongation and inhibition of thrombosis, of edoxaban were comparable to enoxaparin (a low molecular weight heparin, which inhibits both FXa and thrombin) and warfarin (vitamin K antagonist).

Edoxaban inhibited platelet aggregation induced by thrombin, possibly via inhibition of thrombin, since edoxaban did not affect ADP, U46619 or collagen-induced platelet aggregation. In the in vitro studies, recombinant FVIIa, FEIBA (a plasma-derived activated prothrombin complex concentrate) or PPSB-HT (a prothrombin complex concentrate) were used to determine the reversibility of edoxaban-induced anticoagulant activities. Under the conditions tested, reversibility of edoxaban-induced anticoagulation was demonstrated when these plasma factors were added to the mixture. Despite this reversibility, a conclusion cannot be made on the antidote effect of plasma factors in animals or in humans due to limitations of an in vitro study.

Pregnancy Category C is proposed.

5. Clinical Pharmacology/Biopharmaceutics

No issues that would preclude approval were identified. The following text is from the October 31, 2014 signed review:

Key findings are listed below.
Pharmacokinetics and Pharmacodynamics

- *The pharmacokinetics of edoxaban and its main active metabolite following oral administration of single and repeat doses are dose proportional in the range studied in healthy subjects (60 to 120 mg repeat doses).*
- *The absolute bioavailability of edoxaban following oral administration is 62%. It is a substrate of the efflux transporter, P-glycoprotein.*
- *Edoxaban undergoes minimal metabolism. Its main active metabolite is formed via hydrolysis by carboxyesterase 1.*
- *Edoxaban is eliminated mainly as unchanged drug in urine (60% of bioavailable drug) and to a lesser extent via biliary secretion.*
- *Clearance of edoxaban in patients with VTE is similar to that in healthy subjects (~ 30 L/h).*
- *Edoxaban exhibits a concentration dependent effect on anti-FXa activity, prothrombin time, and activated partial thromboplastin time.*

<u>Effect of intrinsic factors</u>

- *A 75% increase in total systemic exposure (AUC) to edoxaban was observed in subjects with moderate and severe renal impairment compared to subjects with normal renal function. A 30% increase in edoxaban AUC was observed in individuals with mild renal impairment compared to subjects with normal renal*

function.
  - *Total systemic exposure to edoxaban was ~ 28% and 15% higher in the elderly and females, respectively.*
- *After accounting for renal function and body weight, age and gender do not affect systemic exposure to edoxaban.*

Effect of extrinsic factors
- *Overall, increased peak and total systemic exposure to edoxaban was observed when edoxaban was co-administered with P-gp inhibitors. About 0.5% of the patients in Hokusai VTE received an adjusted dose because of concomitant therapy with P-gp inhibitors. Trough concentrations in these patients were lower (~10 ng/mL) than those observed in patients who received a full dose (~15 ng/mL).*
  - *Co-administration of rifampin resulted in ~ 40% loss of total systemic edoxaban exposure (AUC). While an increase in systemic exposure to its equipotent active metabolite D21-2393 makes up for this loss in total systemic exposure, it is driven by an increase in peak systemic exposure (Cmax) to D21-2393. At trough (end of inter-dosing interval), there still exists a ~ 80% reduction in exposure to both edoxaban and the metabolite combined.*

Exposure-response relationships
  - *The probability of DVT/PE decreases with increasing edoxaban total systemic exposure.*
  - *The probability of a major bleed increased with increasing edoxaban trough concentrations.*
  - *Alternate dosing in patients with normal renal function is not being proposed as the risk ratio relative to warfarin on the primary efficacy endpoint was 1.05, suggesting that patients achieved comparable benefit on 60 mg edoxaban relative to warfarin.*

6. Microbiology

No issues that would preclude approval were identified.

7. Clinical/Statistical-Efficacy

In support of both indications (to treat DVT/PE [redacted](b) (4)), the Applicant submitted trial results from a single randomized, multicenter, international phase 3 trial, Hokusai VTE. Hokusai VTE was a double dummy, warfarin controlled event driven trial in which one edoxaban dose level (60 mg given once daily for most patients; with 30 mg dose given once daily for a smaller number of patients based on body weight, renal function and concomitant therapy with P-glycoprotein inhibitors) was evaluated. The phase 3 trial met the primary objective of non-inferiority on the symptomatic recurrent venous thromboembolism (VTE) compared to warfarin. For the primary safety endpoint (clinically relevant bleeding) edoxaban was superior to warfarin.

Hokusai VTE randomized 8292 subjects with acute symptomatic VTE to either edoxaban (4143) or warfarin (4149) arms respectively, from 439 sites in 37 countries. Twenty-five subjects in edoxaban arm and 27 subjects in warfarin arm did not receive study treatment. Subjects were stratified by presenting diagnosis: PE with or without DVT vs. DVT only. Within each diagnostic stratum, subjects were further stratified by baseline risk factors (a. temporary risk factors only [such as trauma, surgery, immobilization, estrogen therapy, etc.] vs. b. all others), and need for dose adjustment (body weight ≤ 60 Kg; creatinine clearance [CrCL] between 30 and 50 mL/min inclusive, and concomitant use of the P-gp inhibitors verapamil or quinidine). Subjects were enrolled and treated for 12 months. The mITT population defined as all randomized subjects who received at least one dose of study treatment was the primary efficacy and safety population. Approximately 56% of the mITT enrolled subjects were planned to be treated for up to 12 months. Approximately 17% received a 30 mg dose due to lower body weight, decreased renal function or concomitant medication that included PgP inhibitors.

The primary endpoint was a time to event endpoint consisting of time to first symptomatic recurrent VTE and VTE-related death (i.e., the composite of DVT, non-fatal PE, and fatal PE). This time to event endpoint was defined as time from the day of randomization to the first symptomatic recurrent VTE and VTE-related death experienced by a subject during the 12-month study period. Secondary efficacy endpoints included time to composite of symptomatic recurrent DVT, non-fatal symptomatic recurrent PE, and all-cause mortality.

From the statistical review:
The estimated hazard ratio (HR) for time to symptomatic recurrent VTE or VTE related death was 0.89 (95% confidence interval: 0.70 – 1.13) for the Edoxaban arm versus Warfarin arm. The upper 95% confidence limit of 1.13 demonstrated, with a high confidence level, that treatment with Edoxaban retained at least 91% of the treatment effect of Warfarin. Therefore, non-inferiority was demonstrated in the primary efficacy endpoint for patients treated with Edoxaban versus Warfarin. The median time to symptomatic recurrent VTE or VTE-related death was not reached in either treatment arm.

Edoxaban was not superior to warfarin on further testing for the primary endpoint. Although not powered for statistical testing similar results were seen for patients who were treated with 30 mg and 60 mg doses. The statistical testing proposed superiority testing for the primary endpoint after demonstration of non-inferiority on the combined dosing population (30 and 60 mg). The trial did not demonstrate superiority for that endpoint. Therefore no additional testing of statistical hypotheses for efficacy can be done.

The primary safety endpoint was time to major or clinically relevant non-major (CRNM) bleeding which was proposed to be tested for superiority. .

(b) (4)

From the statistical review:

This statistical reviewer believes the efficacy and safety data from Study Hokusai VTE support the claim of non-inferiority of Edoxaban compared to Warfarin for the treatment of recurrent VTE in patients who have been treated with a parenteral anticoagulant for 5 -10 days.

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The second proposed indication was adequately studied. (b) (4)

The Division of Cardiovascular and Renal Products (DCRP) has performed extensive analyses of the efficacy and safety results of various renal function subgroups (based on cut-off values) for the non-valvular atrial fibrillation indication. As noted by the Clinical Pharmacology review teams and consistent with scientific information with other anticoagulants: 1) the probability of DVT/PE decreases with increasing edoxaban total systemic exposure and 2) the probability of a major bleed increases with increasing edoxaban trough concentrations. Based on their analyses the DCRP and clinical pharmacology reviewers are concerned that the current recommendation of 60 mg for the use in patients with non-valvular atrial fibrillation and whose renal function would be considered normal might result in less than optimal efficacy. This conclusion is based on comparisons of efficacy and safety across renal function subgroups for the ENGAGE trial. Unlike the conclusions for the non-valvular atrial fibrillation use, neither the Division of Hematology Products clinical reviews, the statistical reviews for the VTE indication nor the Clinical Pharmacology review of the Hokusai VTE trial data suggest different dosing recommendations in patients with normal renal function and a VTE other than that studied in the trial.

Differing dose recommendations may be due to inherent differences in underlying disease, in trial design, data collected, concomitant medications, and/or patient populations. Cross-study comparisons can be problematic. However a brief glance at these two trial populations shows the following differences:

Demographic/Medical History	Hokusai VTE	ENGAGE
Age	Mean age 55. 8 years	Mean age 70.6 years
Greater than or equal to 65 years	33%	74%
Male	57%	62%
Hypertension	39%	94%
Renal Impairment (less than 50 mL/min)	7%	13%
Prior warfarin use	Not available	59%
Heart Rhythm Disorder	6.4%	100%
DVT/PE	100%	Less than 2%

These two populations are different by demographics and disease histories. The ENGAGE trial collected and analyzed data appropriate for a trial studying non-valvular atrial fibrillation and the Hokusai VTE trial collected and analyzed data as appropriate for short-term anticoagulant use. The duration of treatment in the trials was different. The ENGAGE trial treatment duration was approximately 2.5 years and the Hokusai VTE trial treatment duration was less than a year. Thus, extrapolating efficacy or safety dose recommendations from the ENGAGE trial to the Hokusai VTE trial is difficult for many reasons.

Additionally, the Clinical Pharmacology review of the Hokusai VTE data suggests that dose reduction recommended and performed for patients with reduced renal function (less than 50 mL/min) is correct. However, the Clinical Pharmacology review recommends not dose reducing for those individuals with lower body weight and concomitant Pgp inhibitor use who use the product for VTE treatment.

For the Hokusai VTE study the Applicant chose the edoxaban dose of 60 mg because the thrombus burden of acute VTE is higher than in the settings of thromboembolism prevention as in patients with non-valvular atrial fibrillation. This decision seems prudent. Prior to finalization of the Hokusai study protocol, the Applicant conducted a prospective analysis and determined that renal function, body weight and co-administration of P-gp inhibitors independently affected edoxaban PK resulting in a higher exposure. Thus, the Applicant prospectively planned that subjects with moderate renal impairment (CrCL between 30 and 50 mL/min), or low body weight (less than or equal to 60 kg) or those taking pre-specified P-gp inhibitors were to be dosed with 30 mg edoxaban daily. As mentioned above, the phase 3 trial met the primary objective of non-inferiority on the primary endpoint of symptomatic recurrent

venous thromboembolism (VTE) compared to warfarin. For the primary safety endpoint (clinically relevant bleeding) edoxaban was superior to warfarin. The FDA performed numerous exploratory subgroup analyses.

The team reviewed the original proposed subgroup with the dosing recommendation of 30 mg. This subgroup constituted less than 20% of the entire VTE trial and the following results were noted: for edoxaban 30 mg -- 22 patients out of 733 patients had a VTE (3%) and for the warfarin group -- 30 patients out of 719 patients had a VTE (4.2%). The efficacy result for the 60 mg edoxaban subgroup was 108 patients out of 3385 patients had a VTE (3.2%) and for the warfarin group 116 patients out of 3403 patients had a VTE (3.4%). The safety results in this subgroup (primary safety endpoint) were for edoxaban 30 mg -- 58 patients out of 733 patients had a bleeding event (7.9%) and for the warfarin group -- 92 patients out of 719 patients had a VTE (12.8%). The safety result (primary safety endpoint) for the 60 mg edoxaban subgroup was 291 patients out of 3385 patients had a safety bleeding event (8.6 %) and for the warfarin group 331 patients out of 3403 patients had a VTE (9.7%). These exploratory analyses support the Applicant's prospective plan.

In the subgroup with reduced edoxaban dosing (30 mg), the largest sub-subgroup were patients weighing less than or equal to 60 kg followed by patients with reduced creatinine clearance and patients on verapamil or quinidine. Further exploratory sub-subgroup analyses revealed that there were 871 subjects (443 in edoxaban and 428 in warfarin arm) who weighed less than 60 Kg and had CrCl level greater than 50 ml/min. Examination of efficacy for this sub-subgroup showed that the percentage of VTE is 2.9% (edoxaban) vs 3.3% (warfarin) and the hazard ratio is 0.92 with a 95% CI of (0.43, 1.95). However the safety analysis of the same sub-subgroup noted that the percentage of major bleeding and/or clinically relevant non-major bleeding is 6.5% (edoxaban) vs 11.9% (warfarin) and the hazard ratio is 0.56 with a 95% CI of (0.35,0.88). My interpretation of these exploratory subgroup analyses for the low body weight group are that the efficacy of edoxaban 30 mg compared with warfarin in this subgroup is comparable to that of the whole population (hazard ratio=0.89 in the whole population), and the safety may be superior with reduced edoxaban dosing for those patients who are of low body weight. Therefore it seems prudent to retain the recommendation for 30 mg dose for this group. The number of patients in the Hokusai VTE trial 30 mg subgroup who took co-concomitant P-gp inhibitors as the only reason for being in the 30 mg dose group is less than 1% and is too small to attempt any conclusion. The following two tables provided by the statistical team provide the data in tabular form.

Table A: Exploratory Efficacy Analyses by subgroups

Subgroups	Edoxaban		Warfarin		HR (95% CI)
	N	Events (%)	N	Events (%)	
GFR Level					
30 – 50 mL/min	268	8 (3.0)	273	16 (5.9)	0.50 (0.21, 1.17)
> 50 ml/min	3850	122 (3.2)	3849	130 (3.4)	0.94 (0.73, 1.20)
Weight					
<= 60 kg	524	15 (2.9)	519	18 (3.5)	0.84 (0.43, 1.68)
> 60 kg	3594	115 (3.2)	3603	128 (3.6)	0.90 (0.70, 1.16)

HR < 1 favors edoxaban; Primary efficacy endpoint: time to VTE or VTE-related death; Subgroup analysis by concomitant use of P-gp inhibitors was not done due to small number of patients in the subgroup receiving concomitant use of P-gp inhibitors.

Table B: Exploratory Safety Analyses by subgroups

Subgroups	Edoxaban		Warfarin		HR (95% CI)
	N	Events (%)	N	Events (%)	
GFR Level					
30 – 50 mL/min	268	28 (10.5)	273	39 (14.3)	0.71 (0.44, 1.15)
> 50 ml/min	3850	321 (8.3)	3849	384 (10.0)	0.82 (0.71, 0.96)
Weight					
<= 60 kg	524	39 (7.4)	519	64 (12.3)	0.60 (0.40, 0.89)
> 60 kg	3594	310 (8.6)	3603	359 (10.0)	0.85 (0.73, 0.99)

HR < 1 favors edoxaban; Primary safety endpoint: time to major bleeding or clinically relevant non-major bleeding; Subgroup analysis by concomitant use of P-gp inhibitors was not done due to small number of patients in the subgroup receiving concomitant use of P-gp inhibitors.

Therefore the dose reduction recommendation as suggested by the Applicant and used in the Hokusai VTE trial will be in the labeling.

8. Safety

The major safety issues identified include bleeding. No intracranial bleeds occurred in the edoxaban arm compared with six in the warfarin arm. Numerically more gastrointestinal bleeding and vaginal bleeding were observed in the edoxaban arm compared with the warfarin arm. Numerically more myocardial infarction cases were observed in the edoxaban arm.

From the DRISK review:

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.

9. Advisory Committee Meeting

The data submitted for review by the Division of Hematology Products did not require a discussion by ODAC regarding the risk/benefit of this anticoagulant.

10. Pediatrics

A deferral has been granted. An agreed upon IPSP exists. There are ongoing negotiations around studies to be conducted.

11. Other Relevant Regulatory Issues

DSI noted deficiencies during inspection. However they concluded in their review that

Data submitted by this sponsor appear acceptable in support of the requested indication.

12. Labeling

All disciplines made recommendations for labeling.

13. Decision/Action/Risk Benefit Assessment

- Recommended regulatory action
  Approval for a revised orig 2 indication
  (b) (4)
- Risk Benefit Assessment
  The trial demonstrated the benefit of edoxaban for the treatment of DVT/PE in patients who have been treated with a parenteral anticoagulant for 5 to 10 days. The major safety issues identified include bleeding. No intracranial bleeds occurred in the edoxaban arm compared with six in the warfarin arm. Numerically more gastrointestinal bleeding and vaginal bleeding events were observed in the edoxaban arm compared with the warfarin arm.
- Recommendation for Post marketing Risk Management Activities
  No REMS for the DHP indication. Routine pharmacovigilance.
- Recommendation for other Post marketing Study Requirements/ Commitments (for final wording please see letter)

Pediatric requirements -- study(ies) – see approval letter for specific

CMC commitments --

1) to make the effort to develop a new dissolution method, which shows greater discriminating ability and follows typical dissolution behavior when implementing changes to the relevant critical material attributes and process parameters,

2) to set the final dissolution acceptance criterion for your drug product using the new method and the overall multipoint dissolution profile data from a minimum of 12 commercial batches (if twelve batches are made), manufactured under the same conditions as those used for the manufactured of the batches used in pivotal clinical trials.

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/s/

ANN T FARRELL
01/08/2015

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Divisional Memo

NDA: 206316 Edoxaban tosylate (Savaysa) for reducing the risk of stroke and systemic embolus in patients with non-valvular atrial fibrillation.

Sponsor: Daiichi Sankyo

Review date: 23 December 2014

Reviewer: N. Stockbridge, M.D., Ph.D., HFD-110

This memo conveys the Division's recommendation to issue an "Approval" letter for this application.

This application has been the subject of reviews of CMC (Khairuzzman, Ghosh, Tang, and Chatterjee; 8 September 2014), biopharmaceutics (Sharp; 9 September 2014), pharmacology/toxicology (Yang 11 August 2014 and Lee 19 August 2014), clinical pharmacology (Menon-Andersen, Moon, Earp, and Schuck; 30 September 2014), clinical effectiveness and safety (Blank and McDowell; 10 October 2014) and statistics (Bai; 20 July 2010). There is also a CDTL memo (Rose; 9 December 2014), with which I am in agreement.

Edoxaban is a reversible inhibitor of Factor Xa, which catalyzes conversion of prothrombin to thrombin in the final common pathway of the intrinsic and extrinsic coagulation systems. In this action, it is similar to rivaroxaban and to apixaban. Edoxaban has three chiral centers (b) (4) There are no issues with its manufacture—as 15-, 30-, and 60-mg tablets. Biopharmaceutics has negotiated a post-marketing commitment to revise the dissolution testing method and obtain representative data with it; there are no other pending manufacturing issues.

There are no unresolved issues with pharmacology/toxicology. The 2-year carcinogenicity data raised no concerns.

Edoxaban is about 60% bioavailable. Absorbed drug is about 60% excreted unchanged in urine. Even mild renal impairment increases AUC by about 30%, moderate-severe impairment by 75%. Prothrombin time tracks plasma levels of drug.

The sole study supporting approval for atrial fibrillation is ENGAGE AF-TIMI 48, a randomized, double-blind, double-dummy study of two doses of edoxaban—30 and 60 mg, with provisions to halve the dose for creatinine clearance <50 mL/min—and warfarin, titrated to INR 2-3. Randomization was stratified for prior warfarin exposure and baseline CHADS2. The study was event-driven, with a primary end point of stroke and systemic embolus, with alpha 0.05 split evenly (an excessively conservative adjustment) between the two dose comparisons for non-inferiority, assessed in the population on treatment or within 3 days thereof.

All agree that both edoxaban dose groups met pre-specified tests for non-inferiority at $p<0.01$, and that neither dose meets nominal statistical significance for superiority to warfarin, although the low dose trends adversely and the high dose trends favorably compared with warfarin.

Despite dose adjustment for renal function, there are clear indications that renal function impacted exposure and that exposure differences impacted both ischemic stroke prevention and risk of bleeding. Various options for addressing this issue are represented in the various reviews. On the whole, the review team favored approval. Dr.

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Lawrence thought instructions for use ought to mirror the conduct of the trial. The clinical reviewers favored approval limited to patients with creatinine clearance <80 mL/min. Clinical pharmacology reviewers favored approval with a higher dose in patients with creatinine clearance >80 mL/min.

Where the relationship between exposure and effect matters and the factors affecting exposure are understood, dose adjustments are common. Although the majority of such adjustments result in a decrease in dose, upwards adjustment to compensate for the effects of metabolic inducers is not rare. Two factors distinguish the Savaysa case. First, the population involved in the adjustment is large, about 37% of the target population, judging from ENGAGE, so it is potentially amenable to direct study. Second, there is a possibly dose-, rather than exposure-, related risk.

That one might be able to study the population with creatinine clearance >80 mL/min does not, in my view, mean one should. The exposure-response relationship is quite clearly described in the clinical pharmacology review, and it is a relationship very similar to ones observed for warfarin and dabigatran. A study is not necessary in order to name an exposure-matching dosing regimen for this population.

GI bleeding is higher with edoxaban than it is with warfarin, as shown in the table below, derived from data in the clinical review:

	E30	E60	W
Major	8	15	12
CRNMB	14	21	13

The table above shows major and clinically relevant non-major GI bleeds per 1000 patient-years. If these were actually all dose-related (which is unlikely, since the rate of major bleeding on 60 mg is nearly the same as it is for warfarin), a further increase in dose from, say, 60 to 90 mg (50%), is unlikely to produce more than a further 50% increase in major GI bleeding, about 8 major bleeds. Against this, the expected decrease in ischemic stroke is about 2 events per 1000 patient-years. This is a bargain I would readily make, but perhaps not everyone would. In any case, I think the ENGAGE data provide an adequate basis for decision-making.

Treatment of AF would likely improve were NOAC doses adjusted to optimize ischemic stroke prevention and bleeding risk, perhaps based on individual preferences for the clinical implications of either type of event. That seems possible for edoxaban, using either an assay for blood levels of active drug or PT, which is linearly correlated to drug level over the relevant exposure range. (b) (4)

In summary, I would approve edoxaban at this point. I would label with dose recommendations of 75 or 90 mg for patients with creatinine clearance over 80 mL/min, 60 or 75 mg for those with creatinine clearance 50-80 mL/min, and 30 or 45 mg for patients with creatinine clearance <50 mL/min. Until the Agency is ready to address tailored dosing for all of these drugs, I would require nothing further of this one.

Reference ID: 3677641

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/s/

NORMAN L STOCKBRIDGE
12/23/2014