CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

206316Orig1Orig2s000

OFFICE DIRECTOR MEMO

Deputy Office Director Decisional Memo

Date	(electronic stamp)
From	Robert Temple, MD
Subject	Deputy Office Director Decisional Memo
NDA #	206316
Applicant Name	Daiichi Sankyo
Date of Submission	1/8/2014
PDUFA Goal Date	1/8/2015
Proprietary Name / Established (USAN) Name	Savaysa/ Edoxaban
Dosage Forms / Strength	15, 30, and 60 mg Tablets
Proposed Indication(s)	SAVAYSA is indicated to reduce the risk of stroke and systemic embolism (SE) in patients with nonvalvular atrial fibrillation (NVAF)
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Melanie Blank (efficacy) Tzu-Yun McDowell (safety)
Statistical Review	John Lawrence
Pharmacology Toxicology Review	Baichun Yang/ Shwu-Luan Lee
CMC Review/OBP Review	Debasis Ghosh/ Akm Khairuzzaman/ Sandra Suarez
Microbiology Review	Steven Donald
Clinical Pharmacology Review	Divya Menon-Andersen/ Young Jin Moon/Justin Earp
OSI	Sharon Gershon
CDTL Review	Martin Rose
OSE/DEpi	Anne Tobenkin
OSE/DMEPA	Denise Baugh/Ting-Ting Guo
OSE/DRISK	Cathy Miller

OND=Office of New Drugs
OPDP=Office of Prescription Drug Products
OSI=Office of Scientific Investigations
CDTL=Cross-Discipline Team Leader
OSE= Office of Surveillance and Epidemiology
DEPi= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management

I. Introduction

The major issues in the evaluation of edoxaban tosylate (Savaysa), and the recent history of assessments of novel oral anticoagulants (NOACs), have been well-summarized in the cross-discipline team leader (CDTL) review by Dr. Rose and the edoxaban data are well described in the primary review by Drs. Blank and McDowell and in Clinical Pharmacology Reviews (Drs. Menon-Andersen, Moon, Earp, Schuck, Madabushi and Florian), and in the Statistics Review (Drs. Lawrence and Hung). In brief, there is no question that the effectiveness of edoxaban has been demonstrated. It was clearly shown to be non-inferior to warfarin for the total stroke (ischemic and hemorrhagic) plus systemic emboli primary endpoint in the ENGAGE AF TIMI48 Trial. The ENGAGE study was a non-inferiority study that compared two doses, 30 mg and 60 mg o.d., to warfarin (INR goal 2-3), with doses modified downward, to half of the 30 or 60 mg, in patients expected to have increased plasma levels (poor renal function, low body weight, or use of metabolic (P-gp) inhibitors which increased Cmax and AUC by 50-80% in phase 1 studies). Trough blood levels of edoxaban were collected in most patients. The study of two doses, use of reduced doses in subsets, and the large amount of available blood level data yield many opportunities for assessment of dose-response and concentration response relationships for the primary endpoint and its major components, ischemic and hemorrhagic stroke, and for bleeding (all major and clinically relevant non-major, or CRNM). It is these concentration response relationships and the reduced effectiveness in ischemic stroke reduction compared to warfarin seen in patients with normal renal function (in contrast to the favorable effect seen in patients with mildly reduced renal function) that pose the major issue in evaluation of this application. Specifically, there appear to be two relatively unusual choices: 1) approval with a highest recommended dose of 60 mg, but with labeling that indicates that edoxaban should not be used in patients with normal renal function, or 2) approval with a recommended dose for those with normal renal function that is greater than 60 mg, the highest dose studied in ENGAGE AF. I will not comment on chemistry, pharmacology-toxicology, microbiology issues, as these have been discussed by Dr. Rose and present no problems.

II. Background

Edoxaban is the third oral anticoagulant that 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. It has been studied as a treatment to reduce the rate of stroke in patients with non-valvular atrial fibrillation and for the treatment of deep vein thrombosis (DVT), and pulmonary embolism (PE), following 5-10 days of initial therapy with a parenteral anticoagulant, a claim included in NDA 206316 that is being reviewed by the Division of Hematology Products, which recommends approval of that use.

To date, the basis for approval of all oral anticoagulants, including the two approved factor Xa inhibitors, rivaroxaban and apixaban, and the competitive direct thrombin inhibitor (DTI) dabigatran, has been a showing of non-inferiority to well-managed warfarin on the rate of all strokes (ischemic and hemorrhagic) plus systemic emboli. Warfarin was shown many years ago to provide a very substantial reduction in these outcomes, about 64%. This calculation is described in the draft guidance on non-inferiority studies. The non-inferiority margin (M_2) to be ruled out for edoxaban in ENGAGE, with our agreement, was 38% (i.e., rule out an HR greater than 1.38 for the event rate on edoxaban vs warfarin). Considering our experience with the available anti-coagulants, there are several areas that need further consideration.

1. All strokes vs separate consideration of thromboembolic (ischemic) and hemorrhagic strokes.

   It is now clear, from findings with all four of the new oral anti-coagulants (NOACs), that these drugs give a marked reduction in hemorrhagic strokes compared to warfarin, which

greatly increases the rate of such strokes. In contrast, although the NOACs are all at least similar to warfarin in effects on ischemic strokes, only dabigatran to date has appeared to be superior. That superiority was markedly dose-related, which also appears true for edoxaban (more below). In considering dose-effect or plasma concentration-effect relationships of NOACs to effects on stroke endpoints it will therefore be critical to look at the two kinds of stroke separately (systemic emboli would be expected to behave like ischemic strokes but are probably too few to affect these considerations). This is not to say that total strokes are not a reasonable primary endpoint, and are what matter to patients and physicians, but to note that the dose and concentration-response relationships can be expected to differ for the two kinds of strokes and, indeed, to move in opposite directions with increased blood levels.

The results on all strokes, ischemic strokes and hemorrhagic strokes, are shown in the following table (Table 1) for the previous approved NOACs.

Table 1: NOAC Results (taken from Approved Labeling)

Dabigatran - RELY

Drug n	Dabigatran 150 6076 n (%)/year	Dabigatran 110 6015 n (%)/year	Warfarin 6022 n (%)/year
95% CIs are shown			
All Stroke	122 (2.0%) HR 0.64 (0.51, 0.81)	171 (3.8%) HR 0.91 (0.74, 1.12)	186 (3.0%)
Ischemic Stroke	103 (1.7%) HR 0.75 (0.58, 0.97)	152 (2.5%) HR 1.13 (0.89, 1.42)	134 (2.2%)
Hemorrhagic Stroke	12 (0.2%) HR 0.26 (0.14, 0.49)	14 (0.2%) HR 0.31 (0.71, 0.56)	45 (0.7%)

Rivaroxaban – ROCKET

Drug n	Rivaroxaban 7081 n (%)/year	Warfarin 7090 n (%)/year
All stroke	253 (3.6%) HR 0.90	281 (4.0%)
Ischemic	206 (2.9%) HR 0.99	208 (2.9%)
Hemorrh	33 (0.5%) HR 0.58	57 (0.8%)

Apixaban – ARISTOTLE

Drug n	Apixaban 9120 n (%/yr)	Warfarin 9081 n (%/yr)
Stroke	199 (1.2%) HR 0.79 (0.66, 0.95)	250 (1.5%)
Ischemic	140 (0.8%) HR 1.02 (0.81, 1.29)	136 (0.8)
Hemorrh + ischemic conversion	52 (0.3%) HR 0.53 (0.35, 0.75)	98 (0.6)
Unknown	14 (0.1%) HR 0.87	17 (0.1)

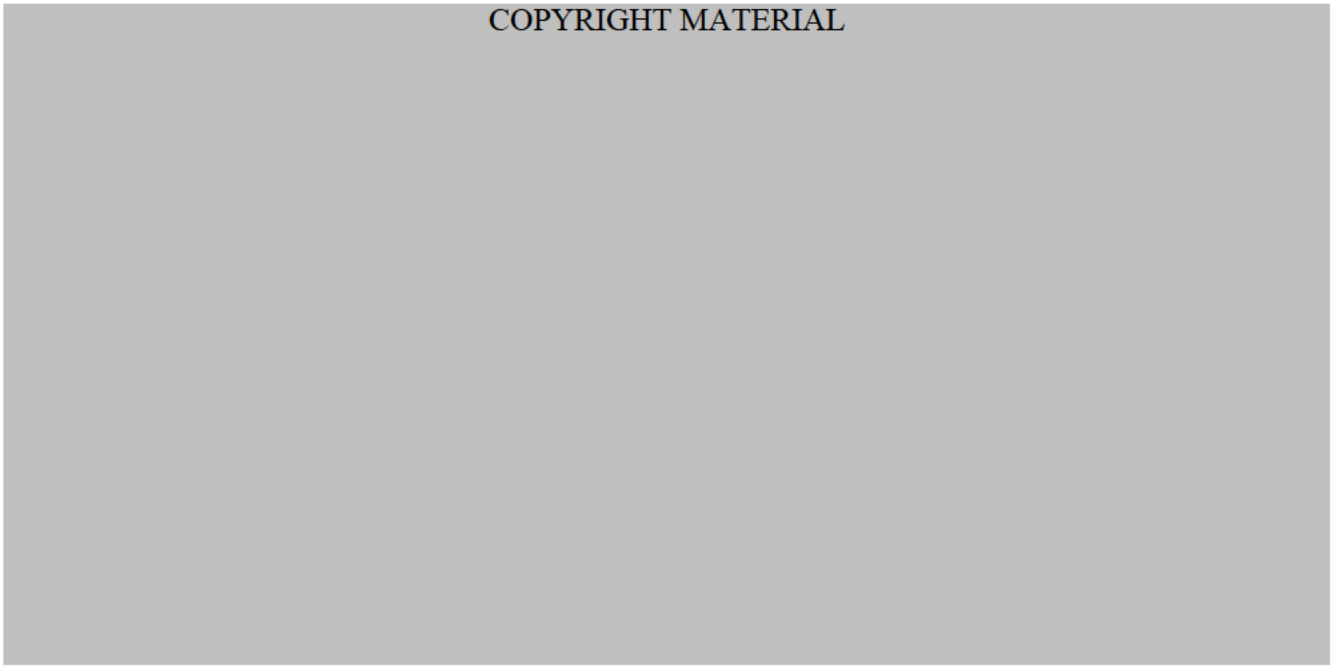
All 3 NOACs showed at least some advantage over warfarin for total strokes, but this was driven primarily (wholly for rivaroxaban and apixaban) by the effect on hemorrhagic stroke. Only dabigatran 150 mg bid showed a nominally significant advantage over warfarin for ischemic stroke. The benefit was clearly dose-related (the low dose was numerically inferior to warfarin) and, as will be shown below, was clearly dabigatran blood level-related. Apixaban and rivaroxaban were more or less numerically identical to warfarin (apixaban numerically worse) for ischemic stroke but had a clear, nominally significant, advantage on hemorrhagic stroke, as did dabigatran. As these NOACs (apixaban and rivaroxaban) had neither > 1 dose nor systemic blood level measurements, there is no ability to assess the relationship of effect to dose or drug blood levels.

As noted, all stroke and systemic emboli remains a reasonable endpoint for comparisons of anti-coagulants but it is apparent that ischemic and hemorrhagic strokes have different (opposite) relationships to the extent of anticoagulation for warfarin and perhaps may also do so for the NOAC's (not for dabigatran, but see edoxaban results below). That being so, it is apparent that studying the relationship of blood level, or some measure of anti-coagulation, (INR, pro-time or others) will be confounded if both kinds of strokes are pooled, although the overall benefit/risk consideration of dose/blood levels will involve consideration of both kinds of stroke as well as bleeding rates.

2. Assessment of blood concentration effect relationships for NOACs and possible assessment of blood levels or anti-coagulant effect in clinical trials and possibly during treatment.

   The dose (concentration) response relationships for NOACs (where they have been measured: dabigatran and edoxaban) and warfarin with respect to ischemic stroke prevention and bleeding are unusual in two respects. First, the effect on ischemic stroke appears to have a drug blood level/anti-coagulant effect threshold, below which stroke rate increases dramatically but above which there seems to be minimal further benefit, i.e., a very "non-linear" relationship. In contrast, major bleeding has a more-or-less continuous (and more-or-less linear) increase in rate with increasing concentrations. There is thus a potential "sweet spot," where levels are above the ischemic stroke-inhibiting threshold, but still low on the bleeding dose-response curve. This has long been recognized for warfarin and the recommended INR of 2-3.5 or 2-3 reflects this, as shown in the following figure, taken from the ACC/AHA/ESC practice guidelines, which shows rates for ischemic stroke and intracranial bleeding, (but rates for overall bleeding show similar increases).

Figure 1: Odds ratio of ischemic stroke/ intracranial bleeding by INR; analysis of observational study in outpatients taking warfarin



The main point here is that the rise in the rate of ischemic stroke is quite steep, more than 3-fold increased with an INR of about 1.5, and it does not drop further with increased INR above 2, while intracranial bleeding rates do not double until INR is 4 or so. The critical importance of INR has led to a standard of care based on the correct range of INR, which must be assessed periodically, a process to which warfarin users have become accustomed, even though it is burdensome.

A perceived gain from the NOACs was what was thought to be the lack of any need to monitor blood levels or anti-coagulation effects, but this needs further consideration. Extensive blood level data have in fact been collected for dabigatran and edoxaban. The relationship of blood levels to stroke and bleeding rates have been analyzed and submitted to FDA for dabigatran, and published by Reilly, et. al. [The Effect Of Dabigatran Plasma Concentrations and Patient Characteristics on the Frequency of Ischemic Stroke and Major Bleeding in Atrial Fibrillation Patients: The RE-LY Trial (Randomized Evaluation of Long-Term Anticoagulation Therapy). J Am Coll Cardiol. 2014 Feb 4;63(4):321-8] and they do not look very different in overall pattern from the relationship for warfarin, with a threshold value for concentration that, if not met, leads to a substantial increase in stroke rates, and a slowly rising rate of bleeding when concentrations are too high. Figures 2, 3, and 4 show curves published by Reilly (fig 2) in 2014 and curves included in the Clinical Pharmacology Review of dabigatran in 2010, signed by Drs. Krudys and Jadhav (figures 3 and 4), showing annualized event rates. Figure 5 shows another version, with outcomes shown as probability (%) of both events (ischemic stroke or life-threatening bleed) per year, which will be useful for comparisons with the edoxaban data.

Figure 2

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Figure 3

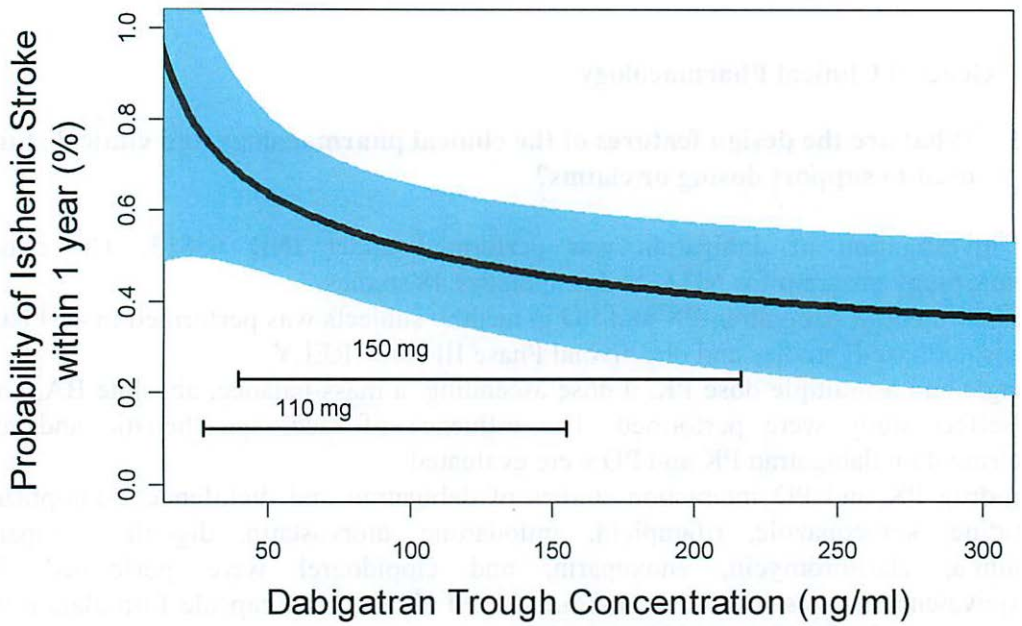


Figure 4

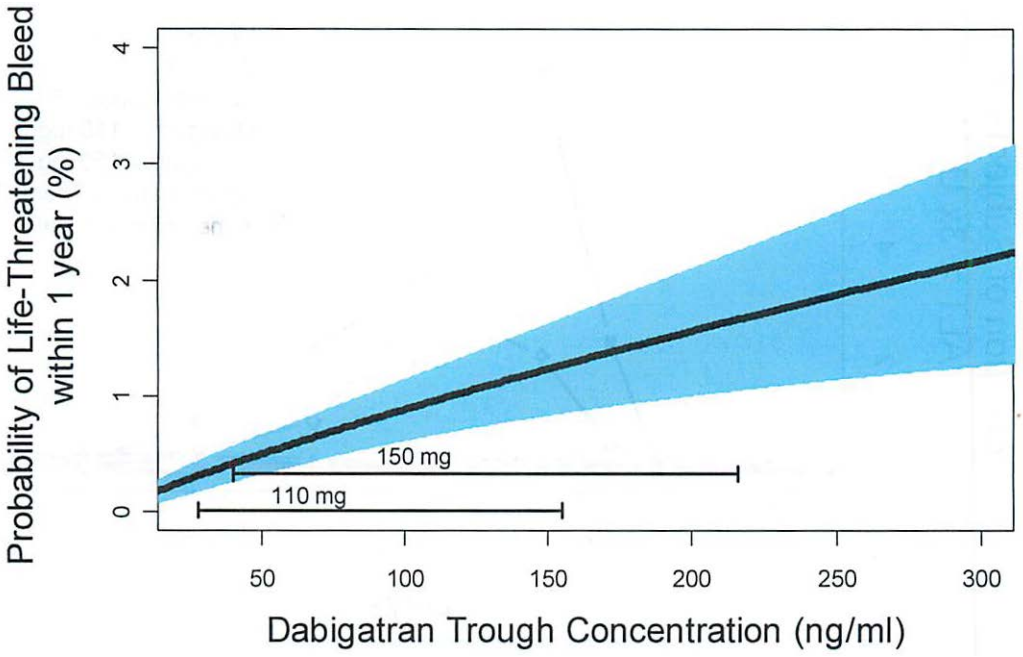
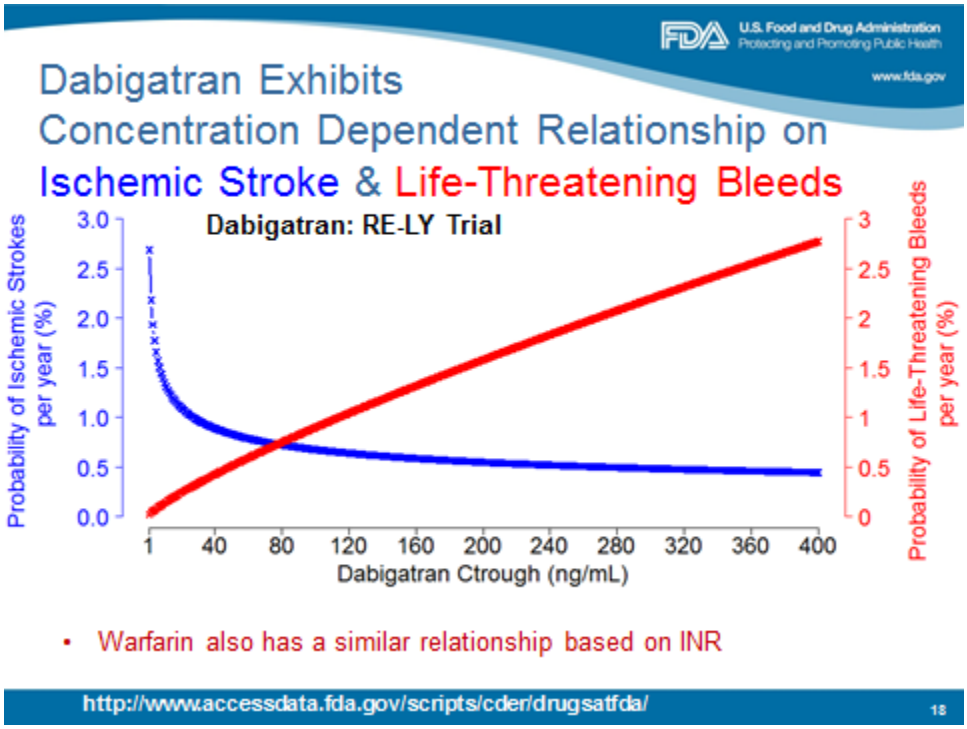


Figure 5



It should also be noted that, as will become important in considering edoxaban, patient renal function affects NOAC blood levels, more for dabigatran (about 80% renally excreted) and edoxaban (about 60%) than rivaroxaban (35%) or apixaban 27%), so that patients with better renal function will have lower blood levels, with potentially reduced effects. Doses were not adjusted for renal function with the 3 drugs. In fact, the influence of renal function has been examined, as described in Dr. Blank's review, p 156 (Table 65). In patients with more normal renal function (CrCL ≥ 80 ml/mm), the comparison to warfarin was generally less favorable. Note that this analysis is for all strokes. We would expect better renal function to increase the HR vs warfarin for ischemic strokes and perhaps lower it for hemorrhagic strokes.

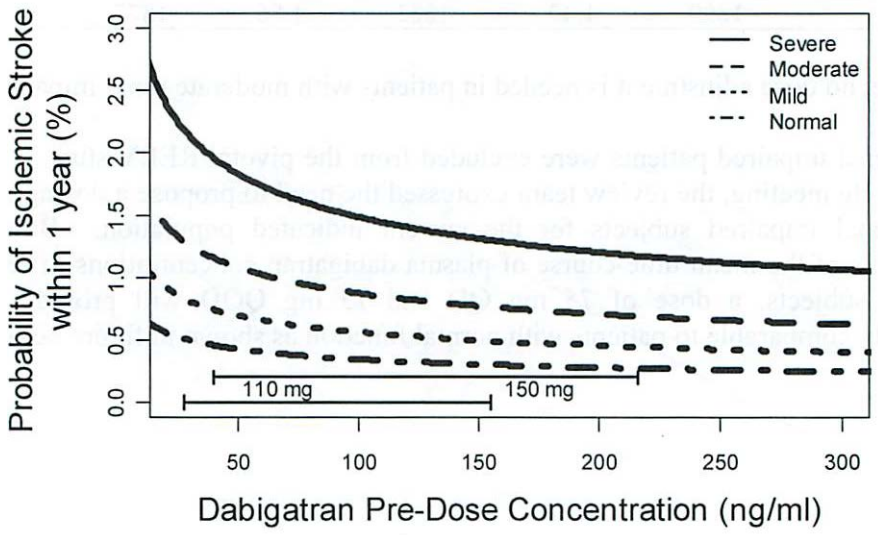
Table 2: Effect on Stroke by Renal Function

Drug (CrCL)	HR for drug vs warfarin
Dabigatran 150 mg - RE-LY	
Overall	0.65
<= 50	0.47
>50 - ≤80	0.65
>=80	0.71
Rivaroxaban - ROCKET AF*	
Overall	0.79
<= 50	0.86
>50 - ≤80	0.73
>80	0.89
Apixaban - ARISTOTLE	
Overall	0.79
<= 50	0.79
>50 - ≤80	0.73
>80	0.88

The "most normal" patients had, in all cases, a numerically higher HR, but the results are "noisy," except for dabigatran, the most renally excreted of the drugs. All of the HRs in the > 80 group remained below 1.0. Again, note that this analysis includes both stroke types.

The dabigatran data suggest a blood level threshold for effectiveness of about 75-150 ng/ml, a level that also gives bleeding rates well below higher concentrations. Note also that other factors can affect stroke and bleeding rates, such as age, renal function (which also affects blood levels) and use of other drugs, notably aspirin. The 2010 dabigatran clinical pharmacology review examined stroke rates in patients grouped by renal function (fig 6) and showed similarly shaped stroke rate-concentration curves, with the effectiveness window still at 75-150 ng/ml.

Figure 6



It is clear from the bars showing distribution of blood levels in figure 2 that the 110 mg bid dose leaves some patients below the effectiveness benefit threshold and in a plasma-concentration area where stroke rates climb dramatically, although it also shows blood levels mostly in a lower bleeding rate territory. The 150 mg bid dose, in contrast, has few patients in a "too low" range, but many more in a higher bleeding range. It is apparent that blood level monitoring could allow all patients to be in the ideal effectiveness zone, say 75-150 ng/ml, which is also a zone that would limit bleeding. Caregivers and patients could, in fact, weigh those benefits and risks in deciding what concentration to "shoot for." To date we have primarily data on the relationship of trough blood levels to outcome, not usable at present as no blood level test is available. Probably more useful would be a measure of anticoagulation that was clearly shown to correlate with blood level.

III. Study of Edoxaban

A. Overall Results

Information supporting the doses needed in the ENGAGE-AF study was derived from study PRT-018, which studied o.d. doses of 30 and 60 mg and b.i.d. doses of 30 and 60 mg, as well as warfarin, in patient groups of about 250. Bleeding events were considered unacceptably high in the two b.i.d. treatments (about twice the rate for o.d. treatments for both all bleeding and major plus clinically relevant (CR) bleeding) and even more increased for major bleeds (5 or 6 vs 0 or 1 on o.d. dosing or warfarin. The o.d. rates were fairly similar to each other, with little suggestion of D/R and rates were not worse than warfarin. In retrospect, as will be seen, a somewhat higher o.d. dose would have been worthwhile, but there was probably no way to know that at the time and it is clear that a critical goal was to attain less bleeding than warfarin.

ENGAGE AF is described fully in the reviews of Drs. Rose, Blank and McDowell as well as analyses by Drs. Lawrence and Hung, with many analyses by Clin Pharmacology. I will not repeat all of this discussion but will identify critical features and potential issues.

The following is taken from Dr. Rose's CDTL memo of December 8, 2014.

Design and results of the pivotal efficacy study:
In support of the proposed indication, the applicant conducted one trial: the ENGAGE AF-TIMI 48 study, a large (21,000+ subjects) trial comparing wo dosing regimens of edoxaban to warfarin to reduce the rate of stroke and systemic embolism.

ENGAGE was an international, randomized, double- blind, double-dummy, event-driven, noninferiority study comparing edoxaban given orally once daily to warfarin titrated to a target INR 2.0 to 3.0 except in Japan, where patients age 70 and above were titrated to an INR of 2.0 – 2.5. Two edoxaban dosing regimens were evaluated: a high exposure regimen, with most patients receiving 60 mg daily, with a reduced dose of 30 mg for patients who met any one or more of 3 dose reduction criteria: creatinine clearance 30 to 50 mL/min; body weight ≤60 kg, or use of specified p-GP inhibiting drugs (dronedarone, verapamil, quinidine); and a low exposure regimen, with most patients receiving 30 mg daily, with a reduced dose of 15 mg daily for those who met the dose reduction criteria described above. Randomization was stratified by dichotomized CHADS2 score (2-3 vs. 4-6) and dose adjustment (full dose or half dose).

ENGAGE enrolled patients with non-valvular atrial fibrillation and a CHADS2 score ≥ 2. This requirement produced a population at higher risk of stroke than patients in RE-LY and ARISTOTLE but at lower risk than those in ROCKET. Study exclusions included: patients who with transient A Fib with a reversible cause; moderate or severe mitral stenosis; intracardiac mass; left ventricular thrombus; a mechanical heart valve; high risk of bleeding from a list of specified causes including dual anti-platelet therapy, other anticoagulants, and use of chronic systemic NSAIDS; creatinine clearance < 30 mL/min,; transaminase ≥ 2X ULN; total bilirubin ≥ 1.5 X ULN; stroke or ACS or PCI within 30 days; and use of specified potent P-gp inhibitors, among others.

A double dummy technique was used in ENGAGE. A point of care device was used to determine INR, with provision of sham INRs to patients randomized to edoxaban. In an attempt to maintain the blind, the protocol also specified that while on study drug, unblinded INR measurements were not to be performed unless the investigator first contacted the TIMI hotline to discuss the situation, except in the setting of a medical emergency. A warfarin dosing algorithm was provided but its use was not mandatory. Intervals for INR determination were not specified; the investigator was to use "good clinical judgment" and keep the INR in the specified therapeutic range.

The trial was event-driven and was designed to establish the non-inferiority of edoxaban to warfarin for the reduction of stroke and systemic embolism. A non-inferiority margin of 1.38 was used, as is customary. Efficacy endpoints and safety endpoints of interest (i.e. bleeding and liver findings) were adjudicated by an independent blinded clinical endpoint committee.

There was a scheduled interim analysis when 50% of the target number of events had occurred, but the only result of this analysis could be dropping of a study group, so there was no reduction in the final alpha. In the final analysis, each edoxaban group was compared to warfarin at the 0.025 level (two-sided) using a Cox model with stratification covariates, assessing non-inferiority of edoxaban to warfarin win an NI margin of 1.38. A hierarchical analysis plan was specified in the event that the 60 mg group was non-inferior to warfarin for the primary endpoint with all analyses involving the comparison of edoxaban 60 mg to warfarin. In the order to be performed the analyses were:

1. superiority for the primary endpoint, p=0.01
2. superiority for time to the composite of stroke/SE/CV death, p=0.01
3. superiority for time to MACE (which includes fatal bleeding as part of CV death), p=0.01
4. superiority for time to stroke/SE/all-cause death, p=0.01

All of these analyses were conducted using a Cox model with the stratification covariates. If any of these analyses did not succeed, subsequent analyses were not to be performed.

There were two major analysis populations: the ITT population (all patients randomized), and the mITT population (all patients who received at least one dose of study drug). There were two major analysis periods: the "overall study period," defined as randomization or first dose of study drug (as specified in the analysis plan) to the CSED visit, and the "on-treatment period," defined as first dose to last dose + 3 days or the CSED, if the patient took study drug up to the CSED.

There was also a per-protocol population, which consisted of mITT patients without major protocol violations. Inclusion in this population was made on the basis of a blinded assessment of whether a major protocol violation occurred. However, this population was not analyzed in any of the analyses in the hierarchy described above.

The primary analysis of NI was determined in the mITT population on-treatment. All the superiority analyses in the hierarchy above were made using the ITT population in the overall study period.

About 7000 patients were randomized to edoxaban 30 and 60 mg, or to warfarin, totaling 21,205, and almost all, 20,970, were analyzed in the per protocol analysis, with a median drug exposure of just over 900 days (about 2.5 years).

Study arms were well-balanced for demographic and risk-related variables, with about 40% ≥ 75 years, 38% women, but with relatively few blacks (1.3%) or Asians (14%). Rates of moderate and mild renal impairment were similar. About 25% of patients had their dose adjusted for one of the 3 reasons noted above. Creatinine clearance was 30-≤ 50, > 50-≤ 80, and > 80 ml/min in 18, 43, and 37% of the subjects, respectively. INR time in range for the warfarin group was a quite good mean of 65%.

Results in the mITT data set are shown below.

Table 3

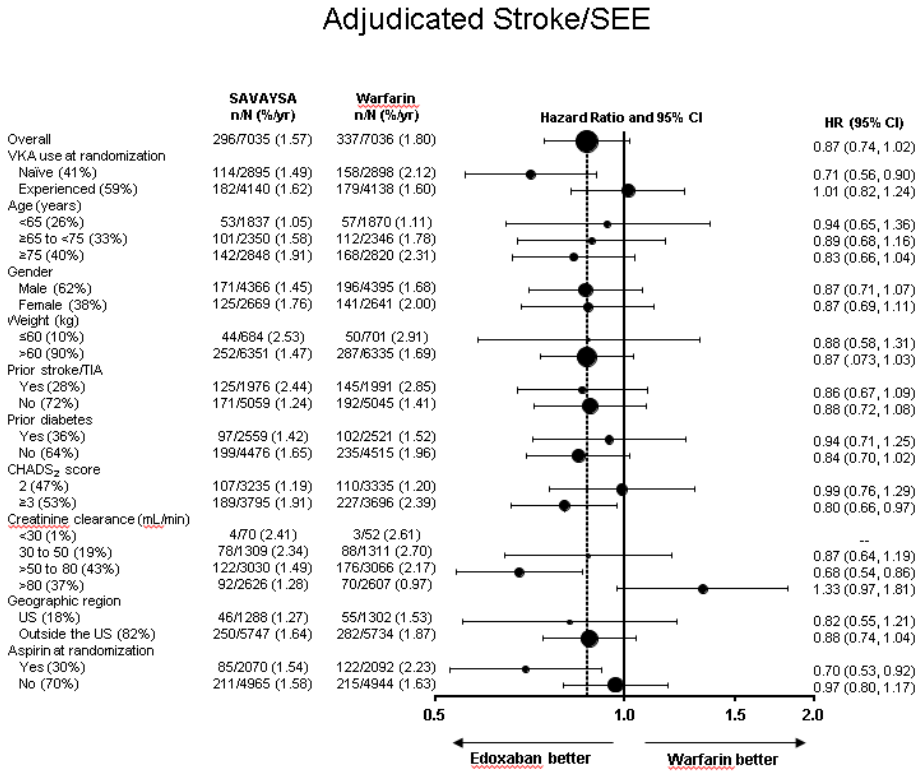
	Edox 30	Edox 60	Warfarin	E 30 vs W	E 60 vs W
Primary: Str & SE	253	182	232	1.07 (0.87, 1.31)*	0.79 (0.63, 0.99)
All Stroke	244	174	219	1.1 (0.91, 1.32)	0.80 (0.66, 0.98)
Ischemic	266	135	144	1.54 (1.25, 1.9)	0.94 (0/75, 1.19)
Hemorrhagic	18	40	76	0.23 (0.14, 0.39)	0.53 (0.36, 0.78)
MI	120	88	105	1.12 (0.86, 1.46)	0.84 (0.64, 1.12)
CV death	195	208	236	0.81 (0.67, 0.98)	0.89 (0.24, 1.07)

* 97.5% CI; others are 95% CIs.

There was a nominally significant advantage for the 60 mg dose on the primary endpoint, and on all stroke and hemorrhagic stroke, and for CV death in the 30 mg group. The planned superiority analysis, however, was on the ITT population for the overall study, including time off drug for the primary endpoint and a superiority finding was to be based on a p-value of 0.01. This was not attained but the nominally significant result in the mITT on treatment analysis in Table 3 is certainly of interest. The hemorrhagic stroke finding is quite strong and is consistent with results of other NOACs.

Examination of results of the primary endpoint in subsets for the 60 mg dose (Figure 7, taken from approved labeling) show generally consistent results, with the striking exception of worse outcome in patients with better renal function, CrCL > 80 ml/minute.

Figure 7: ENGAGE AF-TIMI 48 Study: Primary Efficacy Endpoint by Subgroups (ITT Analysis Set)



Of some potential interest, there was no apparent advantage in patients not receiving aspirin or in experienced users of warfarin.

The principal safety issue with all NOACs is bleeding. See Table 4, from the CDTL review, p 35.

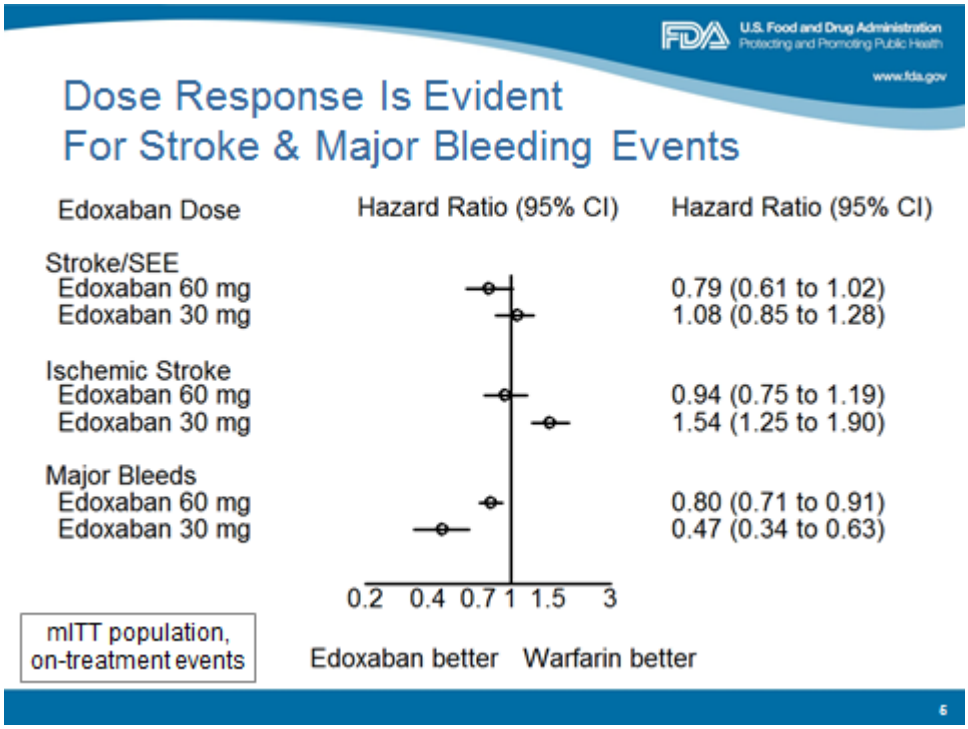
Table 4 – Bleeding

	Edoxaban 30 mg N = 7002 n (per 100 pt-year)	**Edoxaban 60 mg** N = 7012 n (per 100 pt-year)	**Warfarin** N = 7012 n (per 100 pt-year)	**Edoxaban 30mg vs. W** HR (95% CI)	p value	**Edoxaban 60 mg vs. W** HR (95% CI)	p value
ISTH Major Bleeding	254 (1.57)	418 (2.68)	524 (3.34)	0.47 (0.41-0.55)	<.0001	0.80 (0.71-0.91)	0.0009
-GI	129 (0.80)	232 (1.48)	190 (1.20)	0.67 (0.53-0.84)	0.0004	1.24 (1.02-1.50)	0.0309
-Upper GI	88 (0.54)	140 (0.89)	111 (0.70)	0.78 (0.59-1.03)	0.08	1.28 (0.99-1.64)	0.06
-Lower GI	44 (0.27)	96 (0.61)	81 (0.51)	0.54 (0.37-0.77)	0.0009	1.20 (0.89-1.61)	0.2301
-Intracranial (ICH)	41 (0.25)	61 (0.38)	132 (0.82)	0.31 (0.22-0.43)	<.0001	0.47 (0.34-0.63)	<.0001
-Non-ICH	213 (1.32)	359 (2.30)	396 (2.52)	0.52 (0.44-0.62)	<.0001	0.91 (0.79-1.05)	0.2177
-Fatal Bleeding	20 (0.12)	32 (0.20)	59 (0.37)	0.33 (0.20-0.55)	<.0001	0.55 (0.36-0.84)	0.0061
-ICH	12 (0.07)	24 (0.15)	42 (0.26)	0.28 (0.15-0.53)	0.0001	0.58 (0.35-0.95)	0.0319
-Non ICH	8 (0.05)	8 (0.05)	17 (0.11)	0.46 (0.20-1.07)	0.0708	0.48 (0.21-1.10)	0.0822
GUSTO Severe	56 (0.34)	92 (0.58)	175 (1.09)	0.31 (0.23-0.42)	<.0001	0.53 (0.41-0.68)	<.0001
-Non ICH	15 (0.09)	31 (0.20)	44 (0.27)	0.34 (0.19-0.60)	0.0003	0.71(0.45-1.12)	0.1443
-GI	9 (0.06)	21 (0.13)	25 (0.16)	0.36 (0.17-0.76)	0.0077	0.85 (0.47-1.51)	0.58
TIMI Major	106 (0.65)	165 (1.04)	259 (1.63)	0.40 (0.32-0.50)	<.0001	0.64 (0.53-0.78)	<0.0001
-Non ICH	65 (0.40)	104 (0.66)	127 (0.80)	0.50 (0.37-0.68)	<.00001	0.83 (0.64-1.07)	0.1475
-GI	47 (0.29)	80 (0.50)	83 (0.52)	0.56 (0.39-0.80)	0.0013	0.97 (0.71-1.32)	0.8520
CRNM Bleeding	965 (1.44)	1210 (8.32)	1390 (9.65)	0.66 (0.61-0.71)	<0.0001	0.86 (0.80-0.93)	0.0002
Major + CRNM Bld.	1161 (7.68)	1528 (10.64)	1761 (12.39)	0.62 (0.58-0.67)	<0.0001	0.86 (0.80-0.92)	<0.0001
Minor Bleeding	533 (3.52)	604 (4.12)	714 (4.89)	0.72 (0.65-0.81)	<0.0001	0.84 (0.76-0.94)	0.0023

Both doses of edoxaban had lower rates of important bleeding, with the exception of GI bleeding, where edoxaban 60 was nominally significantly worse. The advantage in fatal bleeding was largely because of less intracranial bleeding.

The overall study results by are displayed in the forest plot shown in Figure 8.

Figure 8: Dose-Response for Stroke and Major Bleeding Events



It is clear that the overall results of ENGAGE AF strongly support the effectiveness of edoxaban 60 mg on the primary endpoint of all stroke plus systemic emboli. Technically they could be said to support the 30 mg dose as well, as the upper bound of the primary endpoint HR for that dose is well below 1.38, but the adverse point estimate and clear failure to be nearly as good as warfarin or the 60 mg dose makes approval of that dose unreasonable.

There remains, however, a significant issue. As noted the forest plot of results (Figure 7) suggests a problem in people with normal renal function, who would be expected to have lower blood levels of this substantially renally excreted drug. The next section discusses the results by renal function, principally people with CrCL > 50-80 and those above 80 and above 95 mL/min.

B. Results in patients with Normal and Mildly Impaired Renal Function

Given the significant renal excretion of edoxaban (reflected in the lower dose given to patients with creatinine clearance of 30-50 ml/min (moderate renal impairment), it is not surprising that people with normal renal function have lower edoxaban levels. Whether that will affect the drug response depends on the shape of the concentration-response curve and the likelihood that patients given 60 mg will fall below the level needed for stroke prevention. Dr. Rose has summarized the relevant data on stroke results vs edoxaban blood levels.

That dose/blood level make a difference is clear from Table 3 above, where the 30 mg dose was clearly inferior to edoxaban 60 mg and warfarin for ischemic stroke (although better for hemorrhagic stroke) and inferior to edoxaban 60 mg for overall stroke. Bleeding was, however, as

shown in Table 4, lower on 30 mg, although the reduction in fatal bleeding was small (a difference of 12 events, principally because of the lower rate of intracranial hemorrhage).

As might be expected, given the dose response, a comparison of results in patients on 60 mg with mild renal impairment, who would have higher blood levels, and those with normal function reveals a similar disparity on the primary endpoint and on ischemic stroke, a fairly large difference. Table 5 shows the initial overall analysis by major groups (all patients, CrCL > 50-80, and ≥ 80 mL/min. Table 6 shows data for ischemic and hemorrhagic strokes. The 30 - < 50 ml/min group is not shown, as they had their doses reduced.

Table 5: Primary Endpoint vs Renal Function

Renal Function	Edox 60	Warfarin	HR (95% CI)
>50-<80 ml/min	n = 2985	n = 3030	0.51 (0.38, 0.89)
≥ 80 ml/min	n = 2612	n =2595	1.41 (0.97, 2.05)
All patients	n = 7012	n = 7012	0.79 (0.65, 0.96)

Table 6: Ischemic and Hemorrhagic Stroke Results in Subgroups

Renal Function Subgroup*/STROKE TYPE	Arm	n(N)	Event Rate %/yr	HR (95% CI) vs. W
ISCHEMIC STROKE				
CrCL ≥ 50 to < 80 ml/min (mildly impaired)	Warfarin	83 (3030)	1.23	-
	Edoxaban 60 mg	51 (2985)	0.77	0.62 (0.43, 0.87)
CrCL ≥ 80 ml/min	Warfarin	33 (2595)	0.53	-
	Edoxaban 60 mg	52 (2612)	0.84	1.58 (1.02, 2.45)
HEMORRHAGIC STROKE				
CrCL > 50 to < 80 ml/min (mildly impaired)	Warfarin	45 (3030)	0.66	-
	Edoxaban 60 mg	16 (2985)	0.24	0.36 (0.20, 0.04)
CrCL ≥ 80 ml/min	Warfarin	13 (2595)	0.21	-
	Edoxaban 60 mg	11(2612)	0.18	0.85 (0.38, 1.9)

The inferiority to warfarin on ischemic stroke in the normal renal function group is quite striking. As all involved recognize, examination of subgroups (such as renal function subgroups) is perilous and demands caution, but this is not the typical subgroup analysis, as we already know from the 2 doses studied that there is a concentration-response relationship for edoxaban, which renal function differences would be expected to also produce.

Renal function is not, of course, a dichotomous variable and its relationship to blood levels is surely continuous. The question, therefore, is whether a point can be defined at which it becomes a problem. Again, as we saw with dabigatran, it is helpful to have blood level data in a substantial fraction of patients, as was also the case here.

Clin Pharm has examined the relationship of trough edoxaban levels to ischemic stroke and bleeding rates, as shown in figures 9 and 10, which show concentration-response relationships for severed levels of renal function.

Figure 9

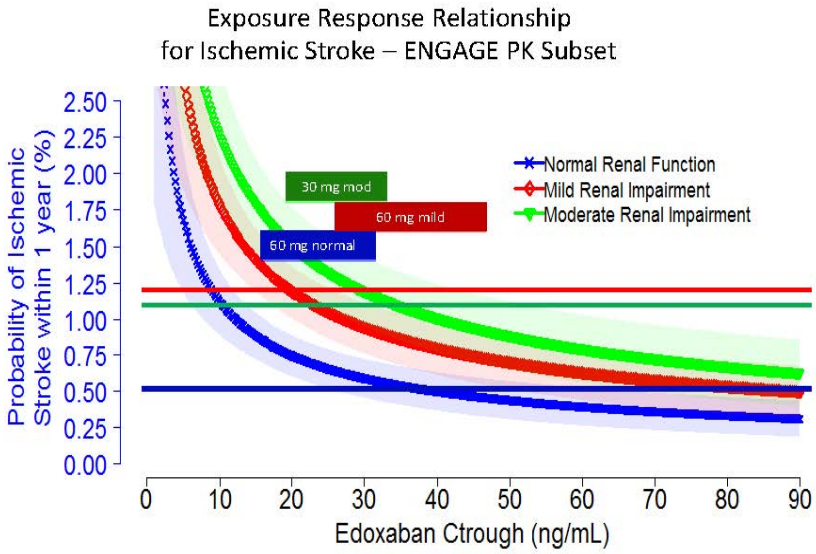


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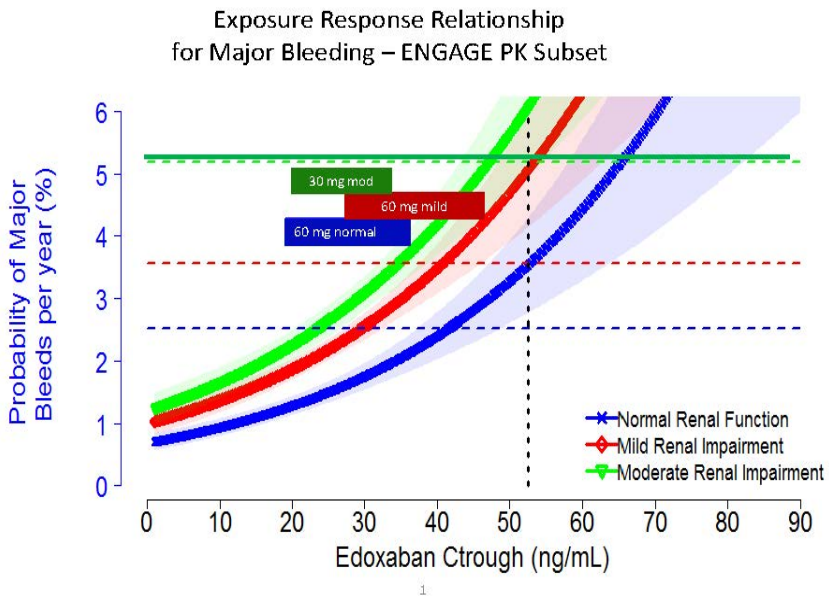
Figure 10

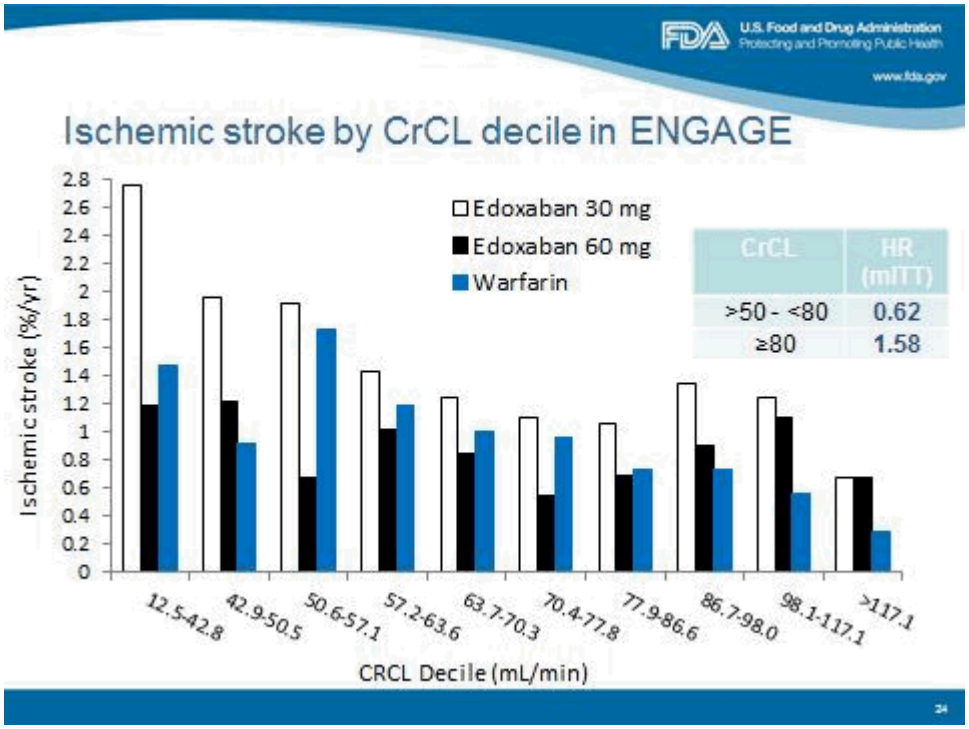


These figures show the ischemic stroke rates in relation to edoxaban trough levels for people with normal, mildly impaired and moderately impaired renal function. The horizontal bars show the distribution of blood levels. Clearly, only the mildly impaired patients given 60 mg are predominately in the desired part of the plasma concentration zone where stroke rates are lower than warfarin. Note that stroke rates on warfarin are renal function dependent.

It is also clear that the patients with mildly abnormal renal function are higher on the bleeding curve than patients with normal renal function.

Results were also examined by various renal function subgroups such as CrCL decile [Figure 11 from Dr. Blank's Advisory Committee presentation (Oct 30, 2014, slide 24) an analysis carried out by Dr. McDowell.] to see whether a population could be defined in which edoxaban 60 mg would do well. Effects in patients with CrCL > 98 seemed clearly adverse, with less clearly adverse results below 98 reasonably similar to warfarin. A cut off of 95 was chosen for labeling.

Figure 11



Overall results for this population, as well as other renal function subsets are shown in Table 7, taken from labeling.

Table 7: Primary Endpoint, Ischemic and Hemorrhagic Stroke Results in Subgroups Based on Renal Function at Baseline (mITT Population, On Treatment)

STROKE TYPE Renal Function Subgroups[a]	Treatment Arm	n (N)	Event Rate (%/yr)	SAVAYSA 60 mg vs. Warfarin HR (95% CI)
PRIMARY ENDPOINT (STROKE/SEE)				
≤ 95 (Indicated Population)	Warfarin	211 (5485)	1.8	
	SAVAYSA 60 mg	142 (5417)	1.2	0.68 (0.55, 0.84)
≤ 50[b]	Warfarin	50 (1356)	2.0	
	SAVAYSA 60 mg	45 (1372)	1.8	0.90 (0.60, 1.34)
> 50 to ≤ 80	Warfarin	135 (3053)	2.0	
	SAVAYSA 60 mg	71 (3020)	1.1	0.53 (0.40, 0.70)
> 80 to ≤ 95	Warfarin	26 (1076)	1.0	
	SAVAYSA 60 mg	26 (1025)	1.1	1.05 (0.61, 1.82)
> 95*	Warfarin	21 (1527)	0.6	
	SAVAYSA 60 mg	40 (1595)	1.0	1.87 (1.10, 3.17)
ISCHEMIC STROKE				
≤ 95 (Indicated Population)	Warfarin	129 (5485)	1.1	
	SAVAYSA 60 mg	102 (5417)	0.9	0.80 (0.62, 1.04)
≤ 50[b]	Warfarin	28 (1356)	1.1	
	SAVAYSA 60 mg	31 (1372)	1.2	1.11 (0.66, 1.84)
> 50 to ≤ 80	Warfarin	83 (3053)	1.2	
	SAVAYSA 60 mg	52 (3020)	0.8	0.63 (0.44, 0.89)
> 80 to ≤ 95	Warfarin	18 (1076)	0.7	
	SAVAYSA 60 mg	19 (1025)	0.8	1.11 (0.58, 2.12)
> 95*	Warfarin	15 (1527)	0.4	
	SAVAYSA 60 mg	33 (1595)	0.9	2.16 (1.17, 3.97)
HEMORRHAGIC STROKE				
≤ 95 (Indicated Population)	Warfarin	70 (5485)	0.6	
	SAVAYSA 60 mg	34 (5417)	0.3	0.50 (0.33, 0.75)
≤ 50[b]	Warfarin	18 (1356)	0.7	
	SAVAYSA 60 mg	12 (1372)	0.5	0.66 (0.32, 1.36)
> 50 to ≤ 80	Warfarin	45 (3053)	0.7	
	SAVAYSA 60 mg	17 (3020)	0.3	0.38 (0.22, 0.67)
> 80 to ≤ 95	Warfarin	7 (1076)	0.3	
	SAVAYSA 60 mg	5 (1025)	0.2	0.76 (0.24, 2.38)
> 95*	Warfarin	6 (1527)	0.2	
	SAVAYSA 60 mg	6 (1595)	0.2	0.98 (0.31, 3.05)

IV. Conclusion

A wide range of views have been expressed by reviewers, the CDTL, Advisory Committee members, and at internal meetings by FDA management. Virtually all have believed that edoxaban should be approved, but with diverse views on just how to do that. In some ways, given our clear knowledge of the plasma concentrations that provide a meaningful reduction in stroke rate and acceptable bleeding, a very attractive option is approval of a dose larger than the 60 mg dose studied in ENGAGE AF, an option supported by Clinical Pharmacology and Drs. Rose and Stockbridge. Clin Pharm has suggested an additional dose between 75 and 90 mg, based on the extensive concentration-response data that are available. These doses have, of course, not been actually studied to any extent and the advisory committee, except for 2 members, did not support such a step. The main concern has been the possibility of a marked increase in GI bleeding, already more common with edoxaban than warfarin. As Dr. Rose notes, however, going from 30 mg to 60 mg (doubling the GI exposure) did not markedly increase GI bleeds (Table 8), at least not more than other bleeds, suggesting no large local effect.

Table 8

Renal Function Category (Creatinine Clearance)	Dose/ Exposure Quartiles	Major GI Bleeds (% events/year)	n/N	Edoxaban Ctrough [min; max]
Moderate Impairment (30-50 mL/min)	15 mg, Q4	1.26 (0.46; 2.72)	6/261	[14.0; 25.0]
	30 mg, Q1,2	0.65 (0.26; 1.33)	7/533	[14.1; 25.5]
Mild Impairment (50-80 mL/min)	30 mg, Q2,3,4	1.12 (0.83; 1.47)	49/1864	[16.5; 37.1]
	60 mg, Q1,2	1.62 (1.19; 2.16)	46/1241	[16.0; 36.6]
Normal (>80 mL/min)	30 mg, Q2,3,4	0.59 (0.39; 0.85)	27/1884	[12.0; 26.6]
	60 mg, Q1,2	0.68 (0.42; 1.04)	21/1261	[10.7; 27.3]

Q1-4: Quartiles of exposure in each dosing cohort
Analyses are limited to subjects with normal/mildly impaired renal function with no dose adjustment and subjects with moderately impaired renal function with a dose adjustment

Dr. Rose concluded that a modest dose increase to 75 mg was very unlikely to lead to a substantial increase in GI or other bleeding, but would put more patients with normal renal function into the right concentration zone. Dr. Stockbridge generally agrees, noting that such dose adjustments are not rare when a drug is taken with a metabolic inducer. Drs. Blank and McDowell favored approval of the 60 mg dose with an effort to limit use in people.

It remains true, however, that there is discomfort with approval of a drug intended for wide use in a relatively fragile population at a never studied dose when there are available alternative NOACs. I do, however, believe the promising results in the mild renal failure group make availability of edoxaban desirable, even if labeling limits use to patients with a defined level of renal function.

It also seems clear from numerous decile and quintile assessments, that although effect on stroke clearly diminishes overall with increasing renal function, the place at which it becomes worse than warfarin is not perfectly clear. It does, however, appear adverse in the patients with CrCL of above 98 ml/min. It is noted that although the best results seem to be in patients with clearly, but mildly, reduced renal

function (CrCL < 80 ml/min), results in the > 80-95 ml/min group appear similar to warfarin. We are therefore approving use of the 60 mg dose in patients with CrCL up to 95 ml/min, and recommending use of an alternative drug in people with better renal function. This will appear in a Boxed Warning and as a limitation of use, with further description in section 14. We did not think it necessary to require further steps, i.e., a REMS.

Finally, I should note that it seems clearer than ever that we should be considering a different dosing paradigm, one that utilizes blood levels or a coagulation parameter to adjust dose, unless a dose can be found that places essentially all patients in a zone that optimizes stroke reduction and bleeding.

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/s/

ROBERT TEMPLE
01/08/2015

Office Director Decisional Memo for Regulatory Action

Date	(electronic stamp)
From	Richard Pazdur, MD
Subject	Office Director Decisional Memo
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) [redacted] (b) (4)
Action/Recommended Action for NME:	Approval for a revised Orig-2 indication for treatment of DVT and PE [redacted] (b) (4)

Material Reviewed/Consulted OND Action Package, including:	
Division Director	Ann Farrell, MD
RPM	Janet Higgins
Medical Officer Review	Saleh Ayache, MD/Kathy Robie-Suh, MD, PhD
Statistical Review	Yun Wang, PhD/Lei Nie, PhD/ Rajeshwari Sridhara, PhD
Pharmacology Toxicology Review	Baichun Yang, PhD/Tomas Papoian, PhD/Shwu Luan Lee, PhD/Haleh Saber, PhD/Paul Brown, PhD
CMC Review/OBP Review	Akm Khairuzzaman, PhD, Debasis Ghosh, PhD, Yubing Tang, PhD, Sharmista Chatterjee, PhD, Olen M Stephens, Ph.D./Sandra Suarez Sharp, PhD/Angelica Dorantes, PhD
Microbiology Review	Steven P. Donald/Stephen E. Langille
Clinical Pharmacology Review	Young Jin Moon, PhD/Julie Bullock, PharmD, Divya Menon-Andersen, PhD, Justin Earp,PhD, Jeffry Florian, PhD
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CDTL Review	Kathy Robie-Suh, MD, PhD
OSE/DMEPA	Denise V. Baugh, PharmD, BCPS/Tingting Gao, PharmD
OSE	John Senior, MD/Carolyn Yancey, MD, Doris Auth, PharmD, Cynthia LaCivita, PharmD

1. Introduction

On January 8, 2014, Daiichi Sankyo submitted NDA 206316 for SAVAYSA (edoxaban tosylate) and new molecular entity and a direct Factor Xa inhibitor for the following indications:

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 (Original – 1)
2) for treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) – under review in the Division of Hematology Products (Original – 2)

(b) (4)

For administrative reasons, the indications were separated as Original-1,Original-2 (b) (4) as identified above under NDA 206316.

2. Background

Several products administered orally or intravenously are approved to treat DVT and PE: 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 initial treatment: rivaroxaban, apixaban, dabigatran, warfarin, heparin, and dalteparin. For all approved products to prevent recurrence (after an initial VTE) an adequate and well-controlled trials with acceptable statistical analysis plans have been conducted.

3. CMC

There are no issues that would preclude approval from the CMC perspective.

According to the CMC review, the 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.

4. Nonclinical Pharmacology/Toxicology

There are no issues that would preclude approval from the nonclinical perspective.

The following is 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

There are no issues that preclude approval from the clinical pharmacology perspective. Key findings from the October 31, 2014, clinical pharmacology review 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.*

Effect of intrinsic factors

- *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

The applicant submitted trial results from a single randomized (N=8292), multicenter, international phase 3 trial (Hokusai VTE) to support of both indications to treat DVT/PE (b) (4)

In support of the claim for treatment of DVT and PE (treatment indication), the trial compared edoxaban 60 mg orally once daily versus warfarin titrated to INR 2.0-3.0 in patients with acute symptomatic VTE in which a total of 8292 patients were randomized. Patients were randomized to edoxaban 30 mg if they met one or more of the following criteria: CrCL ≥ 30 and ≤ 50 mL/min, body weight ≤ 60 kg, or concomitant use of specific P-gp inhibitors. Approximately 17.5% of the patients received a 30 mg per day dose based on their baseline characteristics and an additional 2% had reduction in dose from 60 mg to 30 mg during the course of the study. The primary efficacy endpoint was time to recurrent VTE or VTE-related death during the 12-month study period, and the primary objective was to demonstrate that edoxaban was non-inferior to warfarin. The primary safety endpoint was time to occurrence of major bleeding or clinically relevant non-major bleeding.

The Hokusai VTE study demonstrated that edoxaban was non-inferior to warfarin with respect to both efficacy and safety as presented in Table 1 for the treatment indication.

Based on 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% treatment effect of 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.

Table 1: Primary Efficacy and Safety Analyses in the VTE Study

Primary Endpoint	Edoxaban N = 4118	Warfarin N = 4122	HR (95% CI)
Efficacy: Time to VTE or VTE related death	130 (3.2%) events	146 (3.5%) events	0.89 (0.70, 1.13)
Safety: Time to major bleeding or clinically relevant non-major bleeding	349 (8.5%) events	423 (10.3%) events	0.81 (0.71, 0.94)

HR < 1 favors edoxaban

Edoxaban dose consideration for the treatment of VTE

Another exploratory subgroup analyses was conducted (Tables 2-5) in order to evaluate if a higher dose is warranted for patients with renal impairment. Because restriction to patients with CrCL ≤ 95 mL/min versus those with CrCL > 95 mL/min at baseline (Table 6). All of these subgroup analyses were exploratory. All of the subgroup results were consistent with the overall population results presented in Table 1. Based on the conduct of the VTE study and the exploratory subgroup analyses, OHOP and the Division of Biometrics V's recommendation is that patients with impaired renal function (CrCL between 30-50 mL/min), or ≤ 60 kg body weight, or are using specific P-gp inhibitors, should receive 30 mg edoxaban and all others (including patients with CrCL > 95 mL/min) receive 60 mg per day as studied for the treatment of VTE indication.

Table 2: Exploratory efficacy and safety analyses in subgroup of patients who received Edoxaban 30 mg

Primary Endpoint	Edoxaban N = 733	Warfarin N = 719	HR (95% CI)
Efficacy: Time to VTE or VTE related death	22 (3.0%) events	30 (4.2%) events	0.73 (0.42, 1.26)
Safety: Time to major bleeding or clinically relevant non-major bleeding	58 (7.9%) events	92 (12.8%) events	0.62 (0.44, 0.86)

HR < 1 favors edoxaban

Table 3: Exploratory efficacy and safety analyses in subgroup of patients who received Edoxaban 60 mg

Primary Endpoint	Edoxaban N = 3385	Warfarin N = 3403	HR (95% CI)
Efficacy: Time to VTE or VTE related death	108 (3.2%) events	116 (3.4%) events	0.93 (0.72, 1.21)
Safety: Time to major bleeding or clinically relevant non-major bleeding	291 (8.6%) events	331 (9.7%) events	0.87 (0.74, 1.02)

HR < 1 favors edoxaban

Table 4: Exploratory Efficacy Analyses by subgroups

Subgroups	Edoxaban		Warfarin		HR (95% CI)
	N	Events (%)	N	Events (%)	
CrCL 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 5: Exploratory Safety Analyses by subgroups

Subgroups	Edoxaban		Warfarin		HR (95% CI)
	N	Events (%)	N	Events (%)	
CrCL 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.

Table 6: Exploratory efficacy and safety analyses by CrCL level (≤ 95 mL/min vs. > 95 mL/min)

	Edoxaban		Warfarin		HR (95% CI)
	N	Events (%)	N	Events (%)	
Efficacy: Time to VTE or VTE related death					
≤ 95 mL/min	1935	60 (3.1)	1960	83 (4.2)	0.73 (0.53, 1.02)
> 95 ml/min	2183	70 (3.2)	2162	63 (2.9)	1.10 (0.78, 1.55)
Safety: Time to major bleeding or clinically relevant non-major bleeding					
≤ 95 mL/min	1935	173 (8.9)	1960	243 (12.4)	0.71 (0.58, 0.86)
> 95 ml/min	2183	176 (8.1)	2162	180 (8.3)	0.96 (0.78, 1.18)

HR < 1 favors edoxaban

(b) (4)

The Division of Cardiovascular and Renal Products (DCRP) has performed extensive analyses of efficacy and safety for various renal function subgroups 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 non-valvular atrial fibrillation use in patients with normal renal function might result in less than optimal efficacy based on comparisons of efficacy and safety across renal function subgroups from the ENGAGE trial. The Clinical Pharmacology review of the Hokusai VTE trial does not suggest different dosing recommendations in patients with normal renal function other than that studied in the trial.

Differing dose recommendations may be due to inherent differences in underlying disease, trial design, data collected, concomitant medications, and/or patient populations. Please refer to Dr. Farrell's review for further details.

8. Safety

The major safety issues identified include bleeding. No intracranial bleeds occurred in the edoxaban arm compared with 6 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.

9. Advisory Committee Meeting

This NDA did not require discussion by ODAC regarding the risk/benefit and was not referred to ODAC.

10. Pediatrics

Pediatric studies are deferred and there is an agreed upon iPSP.

11. Decision/Action/Risk Benefit Assessment

- Recommended regulatory action
  -Approval for a revised Orig-2 indication for treatment of DVT and PE
  (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 were observed in the edoxaban arm compared with the warfarin arm. The risk-benefit profile was discussed in the reviews of Drs. Farrell, Robie-Suh and Ayache. Furthermore, all review disciplines recommend approval of the treatment of DVT and PE indication, and I concur with their recommendation.

- Recommendation for Post marketing Risk Management Activities
  A REMS is not necessary for the treatment of DVT and PE indication.

- Recommendation for other Post marketing Study Requirements/ Commitments
  See action letter.

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/s/

TAMY E KIM
01/08/2015

RICHARD PAZDUR
01/08/2015