FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research

Meeting of the Cardiovascular and Renal Drugs Advisory Committee (CRDAC)

FDA White Oak Campus, Building 31, the Great Room (Rm. 1503)
White Oak Conference Center, Silver Spring, Maryland
October 30, 2014

QUESTIONS

As you have heard, there is no disagreement with respect to the overall results of the ENGAGE AF-TIMI 48 trial. It showed non-inferiority (NI margin 1.38) to well-used warfarin (median time in therapeutic range, 66%), and, unlike many cardiovascular (CV) development programs requiring large outcome studies, explored two doses of edoxaban; with dose modification for poor renal function, low weight or certain concomitant therapy.

As with all non-vitamin K dependent oral anticoagulant (NOAC) studies, the primary endpoint was all stroke plus systemic emboli, showing, as Kaplan-Meier (K-M) rates for the two edoxaban doses:

	High (60 mg/30 mg)	**Low (30 mg/15 mg)**	**Warfarin**
NI (on Rx population)	1.18 HR 0.79 (0.63, 0.98)	1.61 HR 1.07 (0.87, 1.31)	1.50 ------
Superiority (ITT, overall study period)	1.57 HR 0.87 (0.74, 1.02) P=0.08	2.04 HR 1.13 (0.98, 1.31) Almost worse, p=0.10	1.80 ------

For the primary endpoint, the high dose was thus nearly superior to warfarin, whereas the low dose was nearly significantly worse, although both clearly met the NI threshold. As there was no marked bleeding excess and bleeding rates were still well below warfarin, it seems hard to support use of a dose < 60 mg. The results are fairly similar to the dabigatran results, which led to approval of only the 150 mg dose. This analysis, however, does not deal with two important issues:

1. The primary endpoint combines thromboembolic and hemorrhagic strokes, which would be expected, based on past experience, to respond differently to dose or blood level. Hemorrhagic strokes might increase with dose or might not change, but thromboembolic strokes would be expected to decrease with increased dose or higher blood level.
2. As edoxaban is renally excreted, renal function could affect blood levels and outcome, particularly when dose was not adjusted (people with normal and mildly reduced renal function both received 60 mg), even though higher blood levels would be expected in the mildly impaired group.

Results for all strokes by renal function (normal and mildly impaired) show a clear difference (we recognize the issues raised by examining subsets) in the 60 mg group.

Renal Function	**Event Rate (%/year)**		**HR vs. W**
Normal	E60 1.07	W 0.76	1.41 (0.97, 2.05)
Mildly impaired	1.04	2.01	0.51 (0.38, 0.69)

Again, recognizing subgroup issues, edoxaban 60 mg (E60) was markedly superior to warfarin in mildly renally impaired patients, but almost significantly worse in patients with normal renal function.

Looking at stroke subtypes, for ischemic stroke:

Renal Function	**Event rate (%/year)**		**HR vs. W**
Normal	E 60 0.84	W 0.53	1.58 (1.02, 2.45)
Mildly impaired	0.77	1.23	0.62 (0.43, 0.87)
Overall	0.87	0.93	0.94 (0.75, 1.19)

For ischemic strokes only (without including the reduction in hemorrhagic strokes) the advantage for edoxaban in patients with mild renal impairment still seems clear, but, again, with removal of hemorrhagic strokes, the effect in patients with normal renal function seems even worse.

We note that two of the three approved NOACs had thromboembolic stroke rates similar to warfarin (only dabigatran 150 mg was better) and that all had lower hemorrhagic stroke rates. Dabigatran 150 mg vs 110 mg showed results fairly similar to the differences seen in normal and impaired renal function with edoxaban; both doses had an advantage for hemorrhagic stroke, but the 110 mg dose was close to significantly inferior on ischemic stroke.

As you have heard, modeling suggests an edoxaban dose of 75 - 90 mg would appear to provide an effect on thromboembolic stroke in patients with normal renal function similar to that seen in mild renal impairment, but these doses have not been given to patients. Although we regularly add lower dose recommendations to labeling to deal with renal or hepatic dysfunction or drug-drug interactions, we can think of no case where we have recommended a larger than studied dose; there are concerns about unexpected toxicity in such cases, although the higher blood levels that would occur have been used in patients; it is thus local effects that raise the principal concern.

Finally, given the availability of several NOACs that work well in people with normal renal function, it might be concluded that there is more work to do before edoxaban is approved.

Given these data and concerns, we have the following questions for the committee:

QUESTIONS (cont.)

---

1. **DISCUSSION:** Please comment on your interpretation of the primary efficacy endpoint, ischemic stroke, and bleeding results in the various subgroups based on renal function in the ENGAGE AF trial. Do you believe the observed differences in outcomes among the renal function subgroups represent the play of chance or differences in exposure? How did you reach your conclusion, and how confident are you in your conclusion?

2. **DISCUSSION:** If edoxaban were approved, would you recommend that a dose higher than 60 mg daily be marketed for patients with normal renal function, based on analyses of the relationships between edoxaban serum concentrations and the major efficacy and safety outcomes in ENGAGE AF?

3. **DISCUSSION:** If edoxaban were approved, it could be marketed at doses of 60 mg and below, as studied in ENGAGE AF, or it could be marketed with some additional higher dose for patients with normal renal function.

   (a) If no dose higher than 60 mg were approved, what steps, if any, would you take to discourage or prevent patients with normal renal function from using the drug for stroke prevention in non-valvular atrial fibrillation?

   (b) If a dose higher than 60 mg were approved, what steps, if any, would you take to ensure that patients with normal renal function are prescribed the higher dose and not the 60-mg dose?

4. **VOTE:** Should edoxaban be approved to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation?
   If you recommend approval, please discuss the following 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.

   If you do not recommend approval, please discuss your thinking.