CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
22-512

OFFICE DIRECTOR MEMO

DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Divisional Memo

NDA: 22512 Dabigatran [redacted] (b) (4) for reducing the risk of stroke and systemic embolus in patients with atrial fibrillation.

Sponsor: Boehringer Ingelheim

Review date: 14 October 2010

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

Distribution: NDA 22512
HFD-110/Blaus/Karkowsky

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

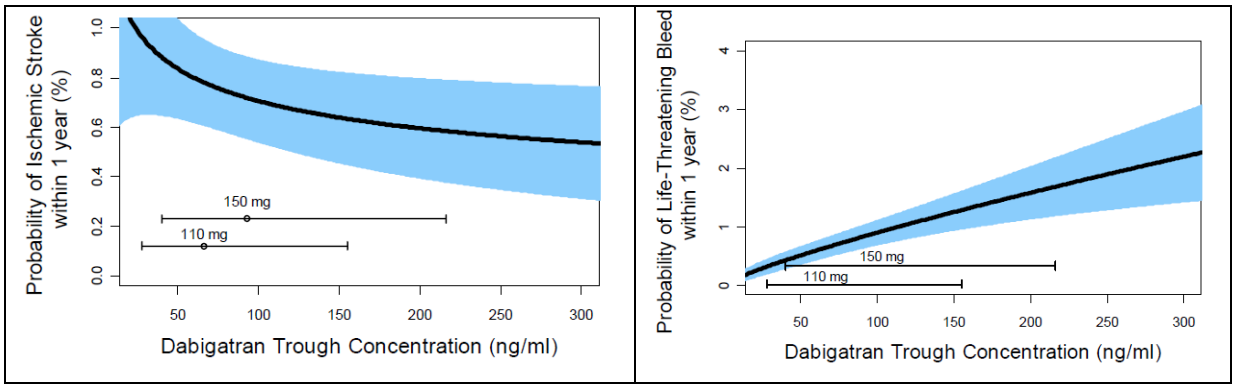
This application has been the subject of reviews of CMC (Jewell and Shiromani; 25 June 2010, 15 September 2010), biopharmaceutics (Ghosh 25 August 2010), pharmacology/toxicology (Harlow; 13 September 2010), clinical pharmacology (Mishina, Hinderling, Hariharan, Hinderling, Krudys, Pacanowski; 17 August 2010 and Krudys; 24 August 2010), clinical effectiveness and safety (Beasley and Thompson; 25 August 2010, 2 September 2010) and statistics (Bai; 20 July 2010). There is also a CDTL memo (Karkowsky; 12 October 2010).

Dabigatran etexilate mesylate has no asymmetric centers and is thus a single isomer. The formulation is coated beads in a capsule. There are no residual CMC issues. Establishment inspections are complete without issue. As usual, we disagree with the sponsor on dissolution specifications.

There are no remaining pharmacology or toxicology issues. The only toxicological finding not clearly attributable to the main action (thrombin inhibitor) is skeletal abnormalities (delayed ossification) and fetal loss in rats; for this there is a low safety factor compared with human exposure.

Dabigatran etexilate mesylate exhibits exposure to dabigatran that is proportional to dose. It is poorly bioavailable (about 5%), but achieves Tmax in about an hour. Meals delay Tmax, but have no effect on exposure; this effect is clinically irrelevant. Etexilate and mesylate are removed by serum esterases. The relevant half-life is about 4 hours; dabigatran and several (active) glucuronide metabolites are renally cleared. Dabigatran is neither metabolized by nor affects P450 enzymes. It is, however, a P-gp substrate, and Clinical Pharmacology recommends further characterization of such effects as post-marketing commitments.

Insight from the RE-LY study (described below) into exposure-response is possible because of inter-subject variability in PK; two doses—110 and 150 mg—were too close to be very helpful. In RE-LY, both stroke prevention and bleeding are related to exposure.



There are no identified genetic factors affecting response—pharmacodynamic or outcomes—to dabigatran.

RE-LY provided the principal data supporting approval. It used open-label, but fairly well managed warfarin and two blinded doses—110 and 150 mg—of dabigatran in patients with non-valvular atrial fibrillation. Subjects were enrolled with at least one additional risk factor—prior stroke or TIA, heart failure, age >75, etc. to increase stroke events; no one wants to restrict use to these patients, but there are no data to address whether risk of bleeding will decline as rapidly as risk of stroke as one moves into a population at lower stroke risk.

The results of RE-LY are described at length in clinical and statistical reviews and in Dr. Karkowsky's memo. I will restrict my comments to a few issues.

INR control was good, but not great. Most subjects in the open-label warfarin arm had at least one interruption in treatment of median duration of about a week, and 18% permanently discontinued warfarin. The median time in therapeutic range (2 < INR < 3) was about 67%. The advantage on strokes of dabigatran 150 mg over warfarin was largely in centers achieving relatively poor INR control[1]. There are several implications of this.

This goes to the issue of the superiority of dabigatran 150 mg to warfarin, but it has no impact on interpretation of dabigatran's effectiveness. Warfarin dosing was not so poor as to question complete loss of or an adverse effect of warfarin on stroke. (In addition, you still have, but, in my view, would not have needed, the observation of clear superiority of the dabigatran 150-mg dose over 110 mg.)

Second, there is little incentive, at least based upon study outcomes, to migrate a patient well controlled on warfarin to dabigatran. (They might still prefer avoidance of INR monitoring, however.)

What doses should be approved? There is general consensus among reviewers that the 150-mg dose of dabigatran is superior to the 110-mg dose, and the Advisory Committee agreed with this assessment. Stroke/SEE event rates were 1.1 per 100 patient-year on dabigatran 150 mg, compared with rates of 1.5 on dabigatran 110 mg and 1.7 per 100 p-y on warfarin. All of the difference between the two dabigatran arms was in ischemic strokes (reduction on 150 mg of 0.4 per 100 p-y), but the difference between dabigatran 150 mg and warfarin was nominally spread across ischemic strokes (reduction of 0.2 per 100 p-y), hemorrhagic strokes (reduction of 0.3 per 100 p-y), and systemic embolus (reduction of 0.1 per 100 p-y).

[1] *See Clinical review of 25 August 2010 page 73ff.*

The price paid for reduction in stroke is largely increased bleeding risk. However, all grades of severity of bleeding included weak criteria. "Major" could mean a 2-g/dL decrease in hemoglobin or a 2-unit transfusion. "Life-threatening" could mean a 5-g/dL decrease in hemoglobin or a 4-unit transfusion. While such events make for a bad day, they did not generally lead to long-term sequelae, and what sequelae there were were captured in other end points of the study.

	Events per 100 patient-years		
	D110	**D150**	**Warf**
Total major bleeds	2.9	3.3	3.6
Total life-threatening bleeds	1.2	1.5	1.9

In addition to bleeding, myocardial infarction was higher on dabigatran—0.7 per 100 p-y on both doses—than on warfarin (0.6 per 100 p-y). I doubt that this small difference is reproducible, but it deserves consideration in tallying the net benefit.

All-cause mortality was lowest on dabigatran 150 mg (3.6 per 100 p-y) and highest on warfarin (4.1 per 100 p-y). Nearly all of difference was in vascular mortality (2.3 vs. 2.7 per 100 p-y). This benefit also was restricted to centers at which INR control was below the median.

In summary, the dabigatran doses compare as follows:

	Events per 100 patient-years		
	D110	**D150**	**Diff**
Mortality Vascular	3.7 2.4	3.6 2.3	-0.1 -0.1
Stroke/SEE	1.5	1.1	-0.4
Total major bleeds Life-threatening	2.9 1.2	3.3 1.5	0.4 0.3
Myocardial infarction	0.7	0.7	0.0

Thus, for every 1000 patients treated for 1 year with dabigatran 150 mg instead of 110 mg, you will have[2] perhaps one fewer death, 4 fewer strokes, and maybe as many as 4 hemorrhagic events likely to require some kind of intervention. The review team, the Advisory Committee, and I concur that the vast majority of patients should be on 150 mg.

The above figure showing ischemic strokes and life-threatening bleeding by exposure suggests that at some point the price paid in bleeding will not be worth the small incremental reduction in strokes. However, the RE-LY net benefit analysis suggests that the optimal dose is above 150 mg. Analyses of the primary end point[3] and of bleeding risk in major subgroups suggest that no subgroup is better off on dabigatran 110 mg—age >75, females, extremes of BMI, low creatinine clearance, or use with aspirin.

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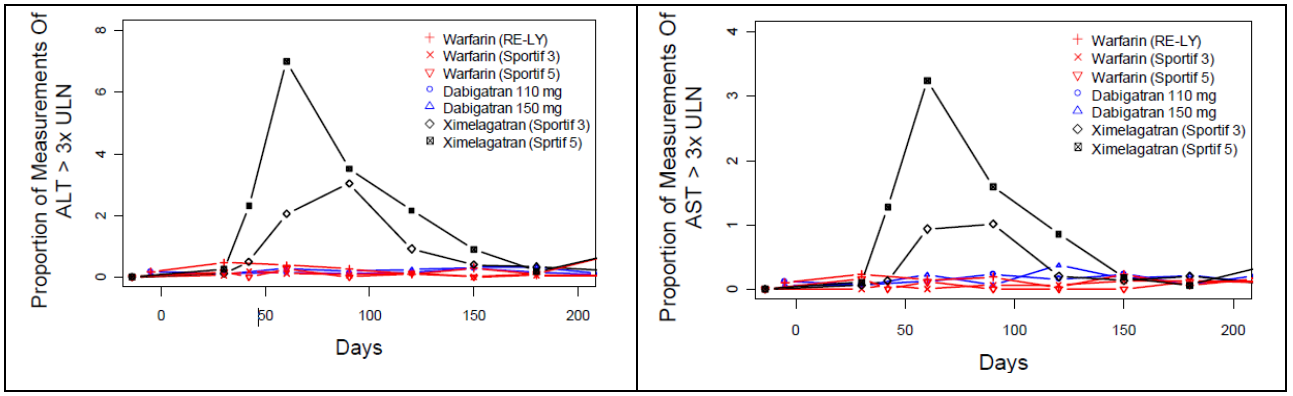
[2] What are shown are nominal results, to the nearest event per 1000 p-y. Confidence limits are ignored. Least reliable are effects on mortality, which, for some analyses performed by the clinical review team, are closer to no difference in rates for the two doses.

[3] See Clinical review of 25 August 2010 page 64.

A suggestion was made at the Advisory Committee to approve the 110-mg dose anyway. The rationale was that patients and physicians are going to observe bleeding on the 150-mg dose, and if they do not have a lower dose, they will stop therapy. I believe that this is a valid concern, but that the proper response is a marketing and educational campaign to get patients and physicians to understand the risk-benefit calculus so that they make the correct therapeutic decision, rather than enabling an incorrect decision.

In summary, if there is a population that would be better off on a dose of 110 mg, it has not been clearly identified. When it is, there will need to be a plan to inhibit inappropriate use of a lower dose.

Hepatoxicity was a significant safety issue with ximelagatran, so considerable effort went into assessment of potential hepatotoxicity with dabigatran. The sponsor's aggressive LFT monitoring in RE-LY led to adjudication of a similar rate of cases on warfarin as on dabigatran. FDA review of these cases found no suggestion of hepatotoxicity. The differences in the two compounds are strikingly shown in Dr. Krudys's review, from which the following figures are copied:



Labeling should say nothing about hepatotoxicity.

Follow-up of anticoagulant activity is generally not needed. However, there is no antidote for dabigatran, so following activity will be useful in that event. Effects of dabigatran can be followed with various clinical assays, as shown below:

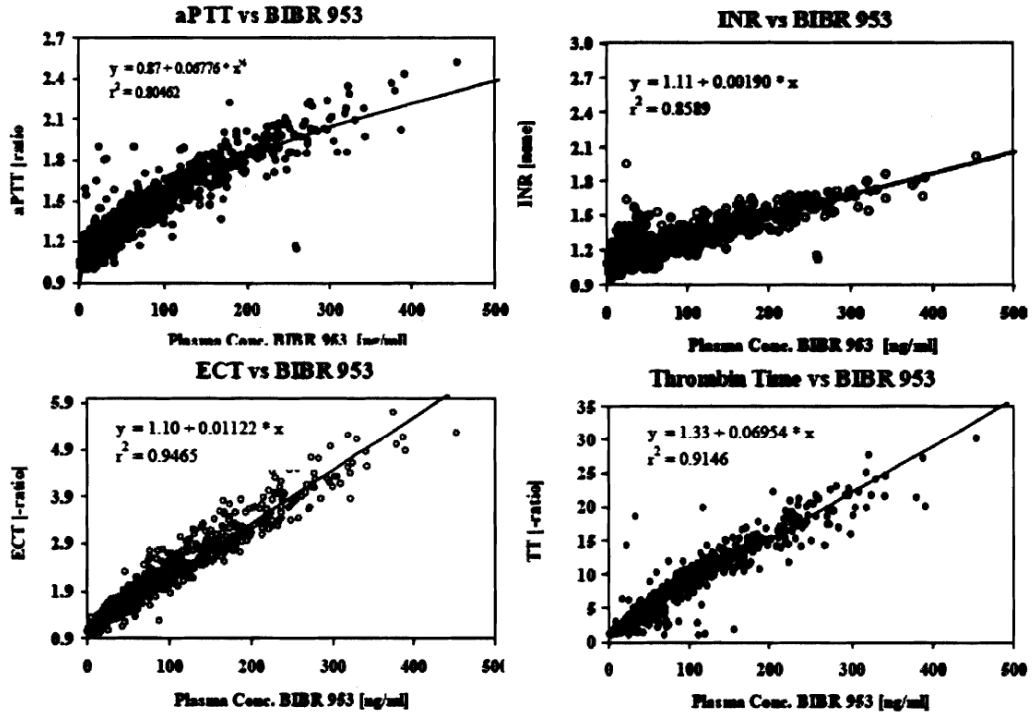


Figure 3. Relationship between dabigatran (BIBR 953) concentration and aPTT, ECT, Thrombin time, and INR

[Source: Sponsor's Clinical Overview (module 2): Figure 2.5.3.2:1]

Of these, it appears that ECT is best, but the others appear adequate and are more widely available.

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/s/

NORMAN L STOCKBRIDGE
10/14/2010