Addendum to Clinical Review for NDA 22-512

Drug: dabigatran (Pradaxa)
Sponsor: Boehringer Ingelheim
Indication: Prevention of stroke and systemic embolism in atrial fibrillation

Division: Division of Cardiovascular and Renal Products
Reviewers: Nhi Beasley

Subject: Risk of myocardial infarction
Date: September 2, 2010

Reviewer's conclusions/recommendations

The rate of myocardial infarction (MI) was higher on dabigatran compared to warfarin in RE-LY. The reason for the higher rate of MI with dabigatran is unclear. Baseline subject characteristics and medication use were similar between treatment arms and do not in part explain the higher rate of MI with dabigatran. The imbalance in MIs was seen on drug as well as off drug. Whether or not the higher rate of MI with dabigatran represents the play of chance, an adverse effect of dabigatran or beneficial effects of warfarin on infarction risk remains unclear. If this is truly a drug-related adverse event, then treating 1000 subjects for one year will cause 2 excess MIs compared to treating with warfarin. This risk should be weighed with the other benefits and risks of dabigatran. At this time, the reviewer recommends describing the higher rate of MI with dabigatran in the label. The sponsor's phase 3 development program in subjects with Acute Coronary Syndromes (ACS) will likely provide a more definitive answer to this question.

Background

Experience with other drugs in its class

The risks of cardiovascular events with ximelagatran, another oral direct thrombin inhibitor, were unclear. There were more coronary artery disease (CAD) adverse events in ximelagatran compared to warfarin treated subjects in the short term studies for prevention of venous thromboembolism (VTE).[1] However, the long-term studies for stroke prevention in atrial fibrillation were inconsistent. SPORTIF III had a greater number of adjudicated acute MIs in ximelagatran compared to warfarin treated subjects, (24 (1.1%) and 3 (0.6%) respectively), as well as more serious cardiac events.[2] In contrast, SPORTIF V had a smaller number of adjudicated MIs in ximelagatran compared to warfarin treated subjects (26 (1.0%) and 37 (1.4%), respectively); serious cardiac events were less in the ximelagatran arm.[2] Lastly, the secondary prevention

[1] See appendix for table of CAD adverse events in EXULT trials.
[2] Taken from SPORTIF trial publications. For SPORTIF V, number given is reported as "on-treatment"; number for SPORTIF III described as ITT. See appendix for table of serious coronary adverse events in SPORTIF trials.

following MI phase 2 study suggested favorable effects of ximelagatran on secondary prevention.[3]

Warfarin

To interpret the findings, it is important to understand the effect of warfarin. As noted in the appendix of the primary review, few MIs were reported in the historical trials that established warfarin's efficacy for the prevention of stroke in subjects with atrial fibrillation. This makes it difficult to ascertain what, if any effect, warfarin has on this outcome. In the Warfarin, Aspirin, Re-Infarction study (WARIS II), an open-label, randomized study of patients hospitalized for acute myocardial infarction and treated with warfarin (target INR 2.8 to 4.2), aspirin (160 mg) or a combination of warfarin (target INR 2.0 to 2.5) plus aspirin (81 mg) post-infarction, a statistically significant reduction in the risk of re-infarction was seen in the warfarin compared to aspirin arm (rate ratio 0.74, 95% CI: 0.55-0.98, p-value <0.03). Relative to the aspirin arm, a statistically significant reduction in re-infarction was also seen in the group treated with warfarin plus aspirin (rate ratio 0.56, 95% CI: 0.41-0.78, p-value <0.001). Whether or not similar warfarin effects would be expected in current practice (i.e., given other advances in anti-platelet therapies) is not clear.

Experience with dabigatran in other treatment programs

Data with dabigatran for the treatment of VTE and following ACS do not suggest an increased risk of MI or ACS. RE-COVER was a phase 3, non-inferiority trial comparing 6 months of dabigatran 150 mg BID to warfarin (adjusted to an INR 2-3) for the treatment of acute VTE. Very few ACS events were observed in the 1273 subjects treated with dabigatran and in the 1266 subjects treated with warfarin.[4] In RE-DEEM, a phase 2, placebo-controlled study of dabigatran dosed twice daily for 6 months in patients on dual antiplatelet therapy after ACS (n~1860), the number of coronary events in the 110 mg and 150 mg dabigatran treatment arms were not greater than in the placebo arm or in subjects on lower doses of dabigatran (see table below). The events were small, however, and the sponsor's categorization of events for the purpose of analyses (non-fatal MI versus CV death) prevents a comparison of total MI event rates (fatal and non-fatal) across treatment arms.

Table 1. CV death, non fatal MI and non-hemorrhagic stroke in RE-DEEM

	Placebo		DE 50		DE 75		DE 110		DE 150	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Treated patients	371	(100)	369	(100)	368	(100)	406	(100)	347	(100)
Patients with event	14	(3.8)	17	(4.6)	18	(4.9)	12	(3.0)	12	(3.5)
Cardiovascular death	9	(2.4)	8	(2.2)	9	(2.5)	5	(1.2)	4	(1.2)
Non-fatal MI	4	(1.1)	9	(2.4)	8	(2.2)	7	(1.7)	8	(2.3)
Non-haemorrhagic stroke	3	(0.8)	0		1	(0.3)	0		0	

Each patient with an event was counted once for the composite endpoint and once for each individual component

[Source: REDEEM Clinical Trial Report dated February 25, 2010, Table 11.4.1.2.2:1]

[3] See appendix for discussion of ESTEEM.

[4] Schulman S et al for the RE-COVER Study Group. NEJM 2009; 361:2342-52.

Review

Reviewer's comment: This addendum to the clinical review for NDA 22-512, (dabigatran for prevention of stroke and systemic embolic events) addresses the risk of MI in the RE-LY trial. Throughout this document, the term MI refers to a clinical MI. All references that include silent MI are clearly stated.

In RE-LY, myocardial infarction was an adjudicated outcome event[5] and was a component of a composite secondary endpoint that included stroke, systemic embolism, pulmonary embolism, and vascular deaths. Though analysis suggested favorable effects of dabigatran (relative to warfarin) on the composite endpoint, the original NDA submission (December 15, 2009) indicated an increased risk of MI with dabigatran as compared to warfarin (Table 2).

Table 2. Relative and absolute risk of MI in RE-LY (original submission)

	D110 v. W HR (95%CI) p-value	D150 v. W HR (95%CI) p-value	D110 v. D150 HR (95%CI) p-value	D110 N (%/yr)	D150 N (%/yr)	W N (%/yr)
Randomized[6]	1.35 (0.98, 1.87) 0.070	1.38 (1.00, 1.91) 0.049	0.98 (0.73, 1.31) 0.88	86 (0.72)	89 (0.74)	63 (0.53)
Safety population[7]	1.40 (0.98, 2.01) 0.066	1.42 (0.99, 2.03) 0.055	0.99 (0.71, 1.37) 0.94	70 (0.68)	71 (0.69)	52 (0.49)

[source: Sponsor's tables 15.2.5:2, 15.2.2.3:1, 15.2.5:1, 15.2.5:3]
In case of recurrent event, the first adjudicated event was considered. The yearly event rate (%/yr) was calculated as the # of subjects with event/subject years *100.

Following the refuse to file letter, the sponsor took measures to confirm the accuracy and integrity of the outcome events, including MI and silent MI (see Appendix). Silent MIs were a predefined outcome event, but because new Q-waves were not reported on the MI case report form, silent MIs were not considered in the sponsor's original analysis. The results of the quality roadmap check are shown in Table 3.

Table 3. Additional adjudicated MI's identified by quality roadmap check

	D110	D150	W
MI	1	0	3
Silent MI	11	8	9

[5] MI definition located in Appendix.
[6] These analyses included all events that occurred between the date of randomization and the date of study termination. Subject-years =sum (date of study termination-date of randomization +1) of all randomized subjects/365.25. Subject-years were 11,900, 12,039, and 11,797 for D110, D150, and W, respectively.
[7] These analyses included all events that occurred from the date of first study medication to the date of last study medication plus 6 days. Subject-years =sum (date of last study drug intake-date of first study drug intake +1) of all treated subjects/365.25. Subject-years were 10,229, 10,253, and 10,661 for D110, D150, and W, respectively.

The new clinical MI findings slightly reduced the risk of MI on dabigatran relative to warfarin and slightly shifted the p-value (Table 4). The absolute risk of MI, however, remained ~0.2% higher with dabigatran (and was not dose dependent).

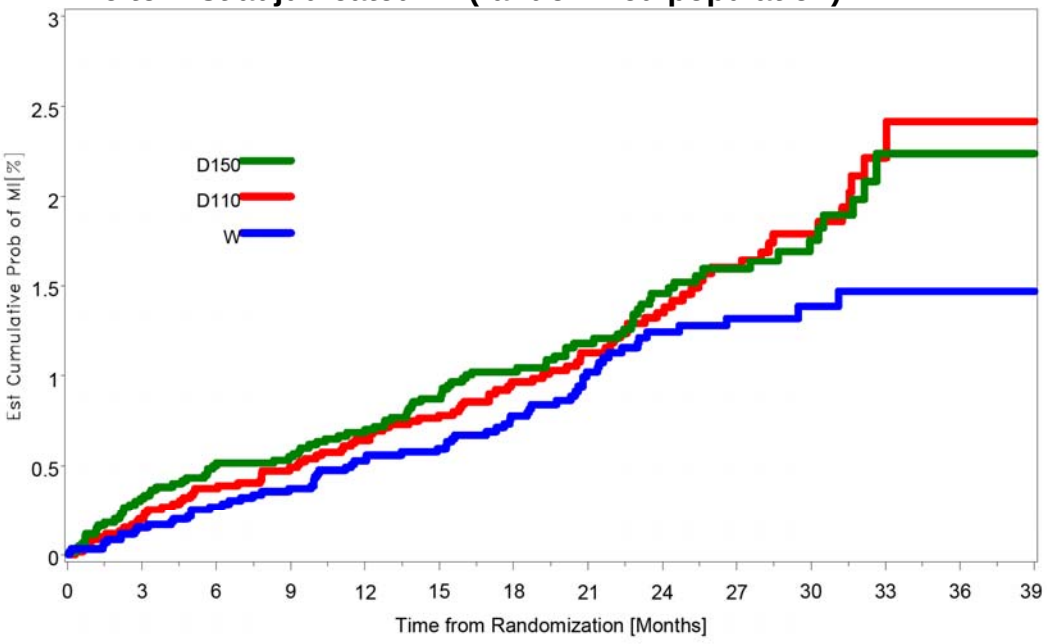
Table 4. Relative and absolute risk of MI in RE-LY (resubmission)

	D110 v. W HR (95%CI) p-value	D150 v. W HR (95%CI) p-value	D110 N (%/yr)	D150 N (%/yr)	W N (%/yr)
MI + silent MI, randomized[8]	1.29 (0.96,1.75) 0.09	1.27 (0.94,1.71) 0.12	98 (0.82)	97 (0.81)	75 (0.64)
MI, randomized	1.30 (0.95, 1.80) 0.10	1.32 (0.96, 1.81) 0.09	87 (0.73)	89 (0.74)	66 (0.56)
MI + silent MI, safety population[9]	1.32 (0.95, 1.84) 0.20	1.30 (0.94, 1.81) 0.12	80 (0.78	79 (0.77)	63 (0.59)

[source: Sponsor's tables 15.2.6.1: 1, 15.2.2.2:1_new, 15.2.5:2_new, 15.2.6.2:1_new, 15.2.6.1: 2, 15.2.6.2:7, resubmission]

The time to first adjudicated MI in the randomized population is shown in Figure 1. The curves are constant over time with the risk in the dabigatran arms greater than warfarin.

Figure 1. Time to first adjudicated MI (randomized population)



No. at risk													
D110	6015	5940	5884	5821	5747	5515	4657	3806	3170	2415	1466	496	85
D150	6076	6006	5941	5872	5802	5564	4718	3851	3237	2441	1489	487	88
W	6022	5952	5896	5821	5760	5469	4651	3728	3108	2369	1376	381	74

[Source: Reviewer's analysis: mi\time mi km (Kaplan Meier analysis of randomized population), sponsor's data set: adjrand]

[8] Subject-years were 11,899, 12,033, and 11,794 for D110, D150, and W, respectively.
[9] Subject-years were 10,242, 10,261, and 10,659 for D110, D150, and W, respectively.

MI occurrence with respect to medication discontinuation
There were numerically more MIs on dabigatran compared to warfarin during treatment, (table below). This numerical imbalance persisted off drug.

Table 5. Number of subjects with MI by time of occurrence from study drug discontinuation

	D110		D150		W	
	n	%	n	%	N	%
Total randomized	6015	(100)	6076	(100)	6022	(100)
Total number of first MIs	87[1]	(1.4)	89	(1.5)	66	(1.1)
MI on drug	56	(0.9)	59	(1.0)	46	(0.8)
MI within 6 days off	13	(0.2)	10	(0.2)	8	(0.1)
MI within 30 days off	15	(0.2)	13	(0.2)	12	(0.2)
MI > 30 days off	15	(0.2)	17	(0.3)	8	(0.1)

[source: adapted from sponsor's table 15.2.5:15, resubmission] 1. The mutually exclusive categories total 86 because 1 MI occurred in a subject randomized but not treated.

Reviewer's comment: There are a few points to consider for the table above. 1. The protocol specified that for dabigatran treatment groups with suspected ACS, dabigatran was to be temporarily discontinued. 2. The determination of the MI event date was not prespecified. Some source documents indicated that the MI date was the hospitalization date; some indicated the MI date was the date of clinically significant cardiac enzymes.

Baseline characteristics
There were no clear baseline differences between treatment groups that might in part explain the imbalance in MIs with dabigatran. Treatment groups were reasonably similar at baseline with respect to the following cardiovascular risk factors: hypertension, diabetes, coronary artery disease (CAD), prior MI, smoking status, age, and total cholesterol.[10,11] Baseline concomitant medications across treatment groups were also reasonably similar (notably, beta blockers, ACE inhibitors, statins, aspirin, clopidogrel, proton pump inhibitors).[10]

MI severity
Information on MI severity with respect to location (anterior or inferior) and post MI heart failure data were not routinely collected, but of the information available (see next table), the numbers suggest that the MIs on dabigatran were worse than the MIs on warfarin (more hospitalizations, more very high enzyme elevations). ECG changes were only captured as new Q-wave or ST-T changes. Characterization of severity by ST elevation or non-ST elevation was not captured. There were very few invasive procedures performed prior to the MI. The incidence of cardiovascular death following recent MI

[10] FDA clinical review
[11] Mean total cholesterol was 180 mg/dL across all treatment arms. LDL cholesterol was not available.[reviewer's analysis]

was low, with 15, 7, and 8 fatal MIs in the dabigatran 110 mg, dabigatran 150 mg, and warfarin groups, respectively [source: sponsor's listing 7.29, submission 132].

Table 6. Summary of MI report

	DE 110mg bid N (%)	DE 150mg bid N (%)	Warfarin N (%)
Total number of adjudicated MIs	90 (100.0)	102 (100.0)	74 (100.0)
Hospitalized for the event	85 (94.4)	93 (91.2)	68 (91.9)
Symptom compatible with acute MI	74 (82.2)	92 (90.2)	61 (82.4)
ECG changes	56 (62.2)	59 (57.8)	49 (66.2)
New Q-wave	10 (11.1)	7 (6.9)	12 (16.2)
ST-T changes	52 (57.8)	56 (54.9)	47 (63.5)
Cardiac enzymes/markers of myocardial necrosis completed	83 (92.2)	95 (93.1)	70 (94.6)
Peak CK	55 (61.1)	63 (61.8)	41 (55.4)
Within normal range	17 (18.9)	17 (16.7)	8 (10.8)
>ULN and <=2xULN	12 (13.3)	18 (17.6)	14 (18.9)
>2xULN and <=3xULN	7 (7.8)	5 (4.9)	4 (5.4)
>3xULN and <=5xULN	6 (6.7)	5 (4.9)	4 (5.4)
>5xULN	13 (14.4)	18 (17.6)	11 (14.9)
Peak CK-MB	52 (57.8)	54 (52.9)	44 (59.5)
Within normal range	9 (10.0)	5 (4.9)	7 (9.5)
>ULN and <=2xULN	11 (12.2)	11 (10.8)	6 (8.1)
>2xULN and <=3xULN	4 (4.4)	6 (5.9)	5 (6.8)
>3xULN and <=5xULN	9 (10.0)	6 (5.9)	7 (9.5)
>5xULN	19 (21.1)	26 (25.5)	19 (25.7)
Troponin	80 (88.9)	91 (89.2)	68 (91.9)
Within normal range	0	2 (2.0)	2 (2.7)
>ULN and <=2xULN	15 (16.7)	13 (12.7)	10 (13.5)
>2xULN and <=3xULN	4 (4.4)	3 (2.9)	6 (8.1)
>3xULN and <=5xULN	7 (7.8)	8 (7.8)	5 (6.8)
>5xULN	54 (60.0)	65 (63.7)	45 (60.8)
Invasive procedure performed prior to the event			
Angio	7 (7.8)	11 (10.8)	7 (9.5)
PCI	5 (5.6)	10 (9.8)	3 (4.1)
CABG	0	0	0
Other	2 (2.2)	4 (3.9)	2 (2.7)

[source: sponsor's table 7.25, appendix 3, submission 132]

The serious adverse event (SAE) data do not indicate more heart failure in the dabigatran arms compared to warfarin, however the reviewer did not link these SAEs to the MI event.

Table 7. Heart failure serious adverse event terms

	D110	D150	W
cardiac failure congestive	83	58	73
cardiac failure	51	62	65
cardiac failure acute	5	1	7
acute LV failure	1	0	1
cardiac failure chronic	0	1	0
cardiomyopathy	2	0	1
congestive cardiomyopathy	2	0	0
ischemic cardiomyopathy	0	1	2
LV dysfunction	2	0	2
LV failure	1	1	0
RV failure	0	1	2
total	**147**	**125**	**153**

[source: adapted from sponsor's table 15.3.2.6:2, resubmission]

Serious adverse events across treatment arms

If dabigatran is likely to cause MI, then one would expect a trend for more unstable angina cases. There were 7, 13, and 5 serious unstable angina reports. Although numerically higher, these numbers are too small to definitively conclude that dabigatran increases the risk of MI.

Appendix

Background

Ximelagatran

The table below shows the greater number of CAD adverse events (MI, "other CAD") in ximelagatran compared to warfarin-treated subjects in the VTE prevention studies. In the EXULT trials, treatment with ximelagatran/warfarin started after total knee replacement and continued for 7 to 12 days.

Table 8. Summary of CAD adverse events in trials of ximelagatran for VTE prevention following total knee replacement

	Exult A		Exult B##		Exult A and B	
Event: N (%)	Exanta N=1526	Warfarin N=759	Exanta N=1151	Warfarin N=1148	Exanta N=2677	Warfarin N=1907
MI	11 (0.72)	1 (0.13)	5 (0.43)	3 (0.26)	16* (0.60)	4* (0.21)
Other CAD (Angina/ischemia)	3 (0.2)	0	1 (0.17)	1 (0.09)	4 (0.15)	1 (0.05)
Total	14 (0.92)	1 (0.13)	6 (0.7)	4 (0.35)	20** (0.75)	5** (0.26)

*p=0.04951; ** p=0.02800

#Excluded 4 patients who did not take study medications, 3 in ximelagatran group (ID: #3206, #7086 and #10944) and 1 in warfarin group (ID: #9089) whose death was also adjudicated by the central adjudication committee as PE.

##one case of sudden death (#15016) in the warfarin group was included as MI and two cases of sudden deaths in the Exanta group (ID: #14366 and 12122) were excluded from the analysis.

Summarized from Module 5, vol. 1 Table 54 and vol. 2 Table 11.3.5.1; vol. 3 Table 55 and vol. 4 Table 11.3.5.1

[Source: Ximelagatran Clinical Review, Table 12]

In the SPORTIF trials, a relationship between ximelagatran and cardiac events was not clearly seen. In contrast, to the VTE trials, the mean duration of use of ximelagatran was upwards of a year in the SPORTIF trials (phase 3 studies of ximelagatran for the prevention of stroke and systemic embolism events in patients with atrial fibrillation). The discrepancies in MI findings were discussed on page 1. The table below also shows a numerically greater number of serious cardiac adverse events in the ximelagatran compared to warfarin arm in SPORTIF III; a finding not seen in SPORTIF V.

Table 9. Cardiac adverse events in SPORTIF trials

	SPORTIF III		SPORTIF V	
	Ximelagatran N=1698	Warfarin N=1699	Ximelagatran N=1953	Warfarin N=1953
MI as AE leading to death	10	3	26	31
MI as SAE not leading to death	25	14	39	48
Angina Pectoris as SAE not leading to death	26	36	34	44
Coronary artery disorder as SAE not leading to death	6	6	20	15

[Source: FDA Clinical Review Ximelagatran for atrial fibrillation]

Numbers represent number of events; AE terms as reported in Review

The findings in ESTEEM, a phase 2 study comparing 6 months of treatment with ximelagatran (4 doses) against placebo in the long-term treatment of patients who had recently been admitted for ST-segment elevation or non-ST-segment myocardial infarction (MI), did not suggest adverse cardiac effects of ximelagatran in this population. In ESTEEM, no increased incidence of MI's was seen in ximelagatran compared to placebo-treated subjects; in fact the numerical imbalance in MI events suggested possible favorable effects of ximelagatran on secondary prevention.

RE-LY trial

Definition of myocardial infarction

Table 10. Definition of myocardial infarction in RE-LY

Efficacy outcome	**Definition**
Myocardial infarction	Depending on whether or not PCI or CABG has been performed, a myocardial infarction (MI) was defined as**:** a. In subjects not undergoing PCI or CABG, at least 2 of the following 3 criteria had to be present: i. Typical prolonged severe chest pain or related symptoms or signs (e.g., ST-changes of T-wave inversion in the ECG) suggestive of MI. ii. Elevation of troponin or CK-MB to more than the upper level of normal (ULN) or, if CK-MB was elevated at baseline, re-elevation to more than 50% increase above the previous level. iii. New significant Q-waves in at least 2 adjacent ECG leads. b. After PCI (within 24 h): Elevation of troponin or CK-MB to more than 3xULN or, if CK-MB was elevated at baseline, re-elevation to more than 3xULN and a more than 50% increase above the previous level, and/or development of significant Q-waves in at least 2 adjacent ECG leads. c. After CABG (within 72 h): Elevation of CK-MB to more than 5xULN or, if CK-MB was elevated at baseline, re-elevation to more than 5xULN and a more than 50% increase above the previous level, and/or development of significant Q-waves in at least 2 adjacent ECG leads. d. Silent MI: retrospectively diagnosed by the appearance of significant new Q-waves between study visits. (In such cases, the date of the event was to be recorded as the midpoint between the 2 study visits) e. Demonstrated by autopsy

Additional notes: Total CK could be used if CK-MB unavailable; significant Q-waves were defined as a duration of at least 0.04 seconds and a depth of more than a quarter of the amplitude of the corresponding R-wave, in at least 2 adjacent leads.

Quality Control Roadmap checks for MI

This process has been described in the clinical review (Section 3.1, Submission quality and integrity). Checks specific to MI included comparison of the MI Case Report Form (CRF) to the adjudication page, a keyword search on various CRFs (i.e., serious adverse events, hospitalization, etc.), and a check for new pathological Q-waves on the study termination CRF.

The silent MI cases were reviewed by “qualified and specially trained clinical monitors”. Cases with obvious symptoms or other indicators of an MI were forwarded from the data center to the clinical site for confirmation/rejection of an event. All re-assessed cases received from the sites as confirmed events were sent to adjudication. Cases with no site response were also sent for adjudication. For silent MIs, the ECG traces were sent straight to adjudication.

Adjudication was done as previously described in the clinical review. All available ECGs were blindly adjudicated by at least two independent cardiologists. The diagnosis of silent MI was based on the study definition.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22512	ORIG-1	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	PRADAXA (DABIGATRAN ETEXILATE MESYLATE)

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/s/

BACH N BEASLEY
09/02/2010