CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202155Orig1s000

SUMMARY REVIEW

Deputy Office Director Decisional Memo

Date	(electronic stamp)
From	Robert Temple, MD
Subject	Deputy Office Director Decisional Memo
NDA/BLA # **Supplement #**	202155
Applicant Name	Bristol-Myers Squibb
Date of Submission	September 28, 2011; Resubmission Sept 17, 2012
PDUFA Goal Date	June 8, 2012 (initial), March 17, 2013
Proprietary Name / **Established (USAN) Name**	Eliquis (apixaban) tablets
Dosage Forms / Strength	Tablet 5 mg and 2.5 mg
Proposed Indication(s)	Reduction in the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review Medical Team Leader Review	Nhi Beasley, PharmD Martin Rose, M.D., JD Thomas Marciniak, MD
Statistical Review	Steve Bai
Pharmacology Toxicology Review	Pat Harlow, Ph.D.
CMC Review/OBP Review	Charles Jewell, William Adams, Young Wang
Microbiology Review	
Clinical Pharmacology Review	Jim Ping Lai, Tzu McDonald
OPDP	Emily Baker – Full Product Labeling Zarna Patel – Patient Labeling
OSI	Sharon Gershon
CDTL Review	Stephen M. Grant, M.D.
OSE/DEpi	
OSE/DMEPA	Morgan Walker, Ray Ford
OSE/DRISK	Danielle Smith
Other – Div Dir Review Dep Dir for Safety Review	

OND=Office of New Drugs
OPDP=Office of Prescription Drug Products
DSI=Division 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

NDA 202155 was submitted on 9/28/2011 and was given a CR on 6/22/12, primarily because of concern with the finding that a substantial fraction of patients might have been given the wrong treatment (active drug instead of placebo or vice versa). The questions we posed in the 6/22/12 CR letter are repeated in the Clinical Review of 12/10/12 (Rose and Beasley) and the applicant's responses described in detail. An addendum to the clinical review dated 12/17/12 addresses a number of additional issues, notably concerns raised by Dr. Marciniak about (b) (4) (in addition to the drug's effect on stroke and systemic embolism, the primary study endpoint) and recommends approval. Dr. Stockbridge's Divisional memo of 12/26/12 summarizes results of two large studies intended to support approval: ARISTOTLE, a non-inferiority study comparing apixaban and warfarin, titrated to INR of 2-3, and AVERROES, a superiority study (on stroke and systemic embolism) comparing apixaban to aspirin in patients with a perceived need to avoid warfarin. Dr. Stockbridge also recommends approval of apixaban.

Whether AVERROES might alone have supported approval, in the absence of a comparison with warfarin (which was known to be superior to aspirin in AF) was discussed in the review of the original submission, but did not need to be resolved as results of ARISTOTLE became available and were submitted in the 9/28/11 NDA.

A late issue has been whether an effect of apixaban on overall survival has been shown with sufficient strength to support inclusion in labeling. Dr. Stockbridge believes it has been credibly shown, but that this conclusion refers most clearly to its advantage over placebo/no treatment, not to a clear advantage over warfarin. He notes similar findings with dabigatran. It is of interest that, once again, as with dabigatran and rivaroxaban, the advantage of apixaban over warfarin on stroke is primarily on hemorrhagic stroke with no substantial advantage of apixaban on ischemic stroke. A mortality benefit thus might arise from an effect of all of the anticoagulants on ischemic stroke (not clearly greater with apixaban than warfarin) and from a lower rate of hemorrhagic strokes than warfarin. Apixaban also showed a clear advantage over warfarin on major bleeding.

II. Effectiveness Results

A. Dispensing Errors

As noted, the principal reason for our CR response was an apparent high rate of dispensing errors, in as much as 7.3% of apixaban patients and 1.2% of warfarin patients. As nicely summarized in Dr. Grant's 6/22/12 review (p 9) there were many opportunities for actual dispensing errors or apparent (recording) errors, magnified by the fact that all patients received two bottles (one apixaban or apixaban-placebo, one warfarin or warfarin-placebo). A principal source of errors was what was written into the electronic CRF (eCRF) as the bottle serial number, possibly reflecting not very clear and readable tear-off labels or perhaps just errors in data entry. Subsequent examination of the actual tear-off labels in two large samples of patients totalling about 35.5% of all bottles dispensed (possible because in the first half of the study the tear-off labels were placed into a paper CRF, and in the second half of the study were retained at the site, where they could subsequently be collected). In the resubmission the applicant included a 12% random sample collected in response to an EMA request and a further 20% random sample in response to the CR letter, ultimately yielding the 35.5% total random sample. As detailed in the Rose/Beasley Dec 10 review, about 99.3% of labels at the random sites were found and 99.9% of those were visually or barcode legible. Using a variety of analyses, including worst case analyses (p 13-22) the reviewers concluded that the findings for the primary endpoint (superiority) and bleeding rates (lower with aspirin) are robust.

B. Study Results

1. ARISTOTLE

a. Primary Endpoint – stroke & systemic embolism.

The ARISTOTLE study is fully described in the Rose/Beasley review dated 5/22/12. Apixaban inhibits Factor X (FXa), which cleaves prothrombin to generate thrombin, which converts fibrinogen to fibrin, the fibrous protein that polymerizes to form a clot, together with platelets. Apixaban has an apparent half-life of about 12 hours after oral administration (lengthened by prolonged gut absorption) and was given twice daily in ARISTOTLE. There is no available drug to reverse its anti-Xa activity.

ARISTOTLE was a randomized, parallel group, double-blind, double-dummy comparison with warfarin titrated to a target INR of 2-3, designed to demonstrate non-inferiority on a composite endpoint of stroke and systemic embolism in subjects with non-vascular AF. The trial included 18,201 patients and was carried out worldwide, about 25% in North America (20% US), 19% in Latin America, 40% in Europe (10% Russia, about 20% Western Europe), and 16% Asia. The trial used a target of 448 adjudicated primary endpoint events. Patients had documented AF or AFI at enrollment or at least twice, 2 weeks apart, in the year preceding enrollment, and at least one risk factor for stroke (age > 75, prior stroke or TIA, CHF or LV dysfunction, diabetes, treated hypertension), which would give them a $CHADS_2$ score of ≥ 1. There were numerous exclusion criteria (see 5/22/12 Rose/Beasley review, p 72-73), most related to recent events, bleeding risk, or other risks. Randomization was stratified by site and by whether patients were already receiving warfarin (naïve or experienced); if they were receiving warfarin, it was stopped till INR fell below 2. The apixaban dose was 5 mg bid in most patients, but 2.5 mg bid in patients with 2 of the following risk factors for bleeding (because of higher blood levels of apixaban): age ≤ 80, weight ≤60 kg, or serum creatinine ≥ 1.5 mg/dl.

Events were very thoroughly assessed and classified (see 5/22/12 Rose/Beasley review). Of note, strokes were classified (CT scan or MRI strongly urged) as ischemic, ischemic with hemorrhagic transformation, hemorrhagic, or uncertain. Major bleeding, another specified study endpoint, was defined as an acute bleed with decrease in Hb of ≥ 2 g/dL, transfusion of ≥ 2 units of packed red calls, bleeding that was intracranial, intraspinal, intraocular, pericardial, intra-articular, intramuscular with compartment syndrome, retroperitoneal, or fatal. Clinically relevant non-major bleeding was bleeding not meeting the above criteria for major bleeding, but that led to hospital admission, need for medical or surgical treatment, or need for a change in anti-thrombotic treatment.

The specified NI margin was an increased HR of 1.38 (the effect of warfarin is quite large, allowing this large margin, representing ruling out a 50% loss of warfarin effect) to be ruled out with 95% CI. As will be seen, superiority was shown, rendering the planned NI margin unimportant. The planned analysis was of time to first event, although the components, as well as many other endpoints, were examined (kind of stroke, AMI, mortality, cause-specific mortality, various kinds of bleeds). Ordered endpoints were:

1. NI for time to stroke/embolism.
2. Superiority for time to stroke/embolism.
3. Superiority for time to major bleeding event.
4. Superiority for time to all-cause mortality.

The primary endpoint was an ITT analysis following all patients during the intended treatment period, but data were clearly not fully available for patients lost to follow-up, making it more like an on-treatment analysis of the primary endpoint. This is apparent from the Rose/Beasley Addendum of 12/17/12 (p 3), which shows the ITT and on-treatment analyses. ITT has far more (almost double) fatal events than the on-treatment analyses (about twice as many), reflecting the ability to assess vital status in patients off-therapy, but there are many fewer additional strokes (about 20% more in the ITT) – which analysis is most appropriate is always a matter of judgment. ITT is often preferred in difference-showing trials because it protects against informative censoring, but given that an effecting agent is no longer given in the post-treatment period, the ITT analysis is conservative (reducing the apparent effect of an effective treatment). This is a serious problem in NI or safety trials, where the ITT analysis, including periods off-treatment, could lead to a finding of no-difference between treatments when there was in fact inferiority.

In any event, the ITT results for the primary endpoint (first event) were (Rose/Beasley, May 22, p 133).

Table 1

	Apixaban (N=9120)	Warfarin (N=9081)	HR	p-value
Stroke or embolism	212	265	0.79	0.0114
Ischemic or unspecified stroke	159	173		
Hemorrhagic stroke	38	76		
Systemic embolism	15	16		

A p-value of 0.0114 is reasonably low, plain evidence of an effect in a NI trial and fairly strong evidence of superiority. It is notable that most of the advantage of apixaban is on hemorrhagic stroke, 38 of the overall advantage of 53, and the percent reduction in hemorrhagic stroke is about 50%, vs about 8% for ischemic stroke.

This is even more striking when the events are broken down further (Rose/Beasley, p 133); note that these are events at any time and total 214 (apixaban) and 267 (warfarin), i.e. 2 additional events for each drug.

Table 2

	Apixaban	Warfarin
Any stroke	199	250
Ischemic stroke	140	136
Ischemic stroke with hemorrhagic conversion	12	20
Hemorrhagic stroke	40	78
Stroke of uncertain type	14	21
Systemic embolism	15	17

In this analysis, essentially all of the advantage of apixaban is on hemorrhagic stroke or ischemic stroke with hemorrhagic conversion, 46 of a total difference of 53.

This is of interest because both rivaroxaban and dabigatran also had their largest effects on hemorrhagic stroke (no data on ischemic stroke with hemorrhagic conversion). There thus may be a tendency for warfarin to induce hemorrhagic strokes that is not fully shared by the newer agents.

Analyses were also conducted of shorter follow-up periods than ITT, notably last dose plus 2, 7, and 30 days. Not surprisingly, given relatively less time on a therapy that had an advantage with the longer follow-up, results are somewhat stronger (Rose/Beasley, 5/22/12, p 134) for analyses of periods (last dose plus 2 or 7 days) with more time on-therapy treatment. As noted, most of the primary endpoint events in the ITT analysis occurred on treatment.)

Table 3

Primary Endpoint	Apixaban (N=9088)	Warfarin (N=9052)	HR	p-value
Last dose + 2 days	176	225	0.77 (0.63, 0.93)	0.008
Last dose + 7 days	184	236	0.76 (0.63, 0.93)	0.006
Last dose + 30 days	218	255	0.84 (0.70, 1.00)	0.05

b. Bleeding

Major bleeding, as defined above, was less frequent on apixaban, largely because of large advantage on intracranial bleeding.

Table 4

	Apixaban	Warfarin	HR	P-value
Major bleeding	327	462	0.69 (0.60-0.80)	< 0.0001
GI	128	141	0.89 (0.70, 1.14)	_____
Intracranial	52	125	0.41 (6.30, 0.57)	_____
Intra-ocular	32	22	1.42 (0.83, 2.45)	_____
Fatal	8	11	0.72 (0.19, 1.79)	_____

c. Mortality

There has been considerable discussion of the mortality findings in ARISTOTLE. As noted, all cause mortality was a specified secondary endpoint and, as all prior endpoints were successful, it could be considered.

The mortality results for the ITT analysis are shown in the following table (Rose/Beasley, 5/22/12, p 137).

Table 5

Endpoint	Apixaban (N=9120)	Warfarin (N=9081)	HR (95% CI)	P
All-cause death	603	669	0.89 (0.80, 1.00)	0.0465
CV death (Caused by ↓)	308	344	0.89 (0.76, 1.04)	-
Stroke	38	65	-	-
Systemic embolism	1	2	-	-
MI	21	17	-	-
Sudden death	126	129	-	-
Heart failure	76	92	-	-
Other CV cause	23	22	-	-
Unobserved death	23	17	-	-
Non-CV death (Caused by ↓)	196	208	0.93 (0.77, 1.13)	-
Bleeding	15	17	-	-
Malignancy	60	66	-	-
Infection	67	52	-	-
Trauma	7	13	-	-
Respiratory failure	19	35	-	-
Other non-CV cause	28	25	-	-
Unknown cause of death	99	117	0.84 (0.64, 1.09)	-

The deaths have some notable features:

1. Most, but by no means all, of the advantage (difference of 66) is for CV deaths (diff = 36) and almost all of that difference (27/36 or 75%) is the difference in fatal stroke, a very plausible advantage for apixaban.
2. The nominal p-value is driven across p=0.05 by the addition of the non-CV deaths, a difference of 12, and the unknown cause deaths, a difference of 18. The non-CV deaths are not plausibly affected by apixaban, but it is likely that the unknowns include some undetected CV deaths, (CV plus unknown would have a difference of 54, and an HR of about 0.88, probably nominally significant (although I did not calculate it).
3. A nominally significant effect on CV deaths would plainly have been a more persuasive finding (although that was not the identified secondary endpoint).
4. Many of the deaths occurred long off therapy, as an analysis by Rose/Beasley (addendum 12/17/12) shows. This analysis examines overall mortality results for populations on therapy, or 7 or 30 days off therapy, shown in table below. Primary endpoint events are included also, for comparison purposes.

Table 6

	Apixaban	Warfarin	Apixaban vs. Warfarin		
Event[1]	n/N	n/N	HR	95% CI	p-value
Death ITT	603 / 9120	669 / 9081	0.89	(0.80, 1.00)	0.0465
Death Tx	265 / 9088	296 / 9052	0.87	(0.74, 1.03)	0.1130
Death TxLD+7	330 / 9088	372 / 9052	0.87	(0.75, 1.00)	0.0555
Death TxLD+30	429 / 9088	471 / 9052	0.89	(0.78, 1.01)	0.0763
Stroke SE ITT	212 / 9120	265 / 9081	0.79	(0.66, 0.95)	0.0114
Stroke SE Tx	176 / 9088	225 / 9052	0.77	(0.63, 0.93)	0.0080
Stroke SE TxLD+7	184 / 9088	236 / 9052	0.76	(0.63, 0.93)	0.0060
Stroke SE TxLD+30	218 / 9088	255 / 9052	0.84	(0.70, 1.00)	0.0526

As noted above, the table shows that the on-therapy results (or on-therapy plus 7 days) look stronger for the primary endpoint (not surprising, as talking the drug provides the benefit) and most of the events occur on therapy (perhaps because off-therapy strokes, for patients no longer participating actively, are simply not reported). In contrast, a very large number of deaths occur off drug, not on face plausibly related to treatment.

Dr. Rose explains why the on-therapy death effect seems weaker, however, in his (12/17/12, p 5) addendum. He shows that in 102 patients with a fatal stroke (on apixaban or warfarin), the stroke occurred at the time of discontinuation or within one day in 71%. Their deaths, however, occurred after the stroke in about 70% of patients, although 55% occurred within 7 days. This could explain why treatment plus 30 days adds relatively few events to the primary endpoint (about 18%) but much more (about 60%) to mortality; i.e. people who stop treatment with a stroke are relatively likely to die. As Dr. Rose notes, a similar difference between post-treatment primary endpoint events and post-treatment deaths was seen with rivaroxaban (ROCKET) and dabigatran (RE-LY).

All in all, these data suggest that looking only at on-treatment deaths will miss relevant fatal events but will be reasonably good for examining the primary endpoint (p-value is 0.008, compared to 0.0114 for ITT).

The evidence for an overall mortality advantage for apixaban is thus statistically marginal, but marginal mortality findings should not be dismissed. In the present case the finding is strengthened by the observation that virtually all of the advantage of apixaban is on fatal stroke, and the effect of apixaban on stroke, especially hemorrhagic stroke or hemorrhagic conversion, is its principal advantage over warfarin, lending the mortality finding greater credibility. Dr. Rose finds this consistency, as well as the significant effect on overall mortality, supportive of the finding.

Dr. Stockbridge, noting data suggesting, albeit not proving, that warfarin has a mortality effect, considers the mortality data supportive of a mortality effect compared to no treatment, but not necessarily a clear advantage over warfarin. Dr. Marciniak (review 12/17/12) has collected data on warfarin trials (p 7 of review) and finds that it is, on its face, not very strong. Three of 6 trials show RR close to or above 1, with only 1 (BAATAF) showing a significant effect and 2 showing a "lean." It is also noteworthy that on pure thrombotic strokes, the advantage of apixaban is relatively small, adding little to whatever warfarin does. Apixaban's mortality advantage, if real, most probably occurs because it does NOT cause as much intracranial hemorrhage.

d. Other Issues

Dr. Marciniak (review dated 12/12/12) considers loss to follow-up and the marginal mortality finding a reason not to include that claim explicitly in indications, a point Drs. Rose and Stockbridge concur in. All agree that the overall findings for stroke and systemic embolism are strong. That leaves open the question of what to say about the data in section 14 (Clinical Studies), discussed further below.

2. AVERROES

   AVERROES was a randomized, double-blind, double-dummy comparison of apixaban 5 mg bid to aspirin 81-324 mg in 5598 patients not taking coumadin because it was shown or expected to be unsuitable; patients had risk factors for stroke similar to ARISTOTLE. The endpoint was the rate of stroke and systemic embolus, with secondary endpoints including MI and vascular death. Results are shown below; essentially all of the difference was on stroke/SE (a difference of 61 events) with MI and vascular death adding little (difference of 65). All cause mortality favored apixaban but was not statistically significant (note, however, that the study was stopped early).

Table 7

	Apixaban (N = 2807)	Aspirin (N = 2791)	HR	p-value
Stroke/SE	51	113	0.45 (0.32, 0.62)	< 0.00001
Stroke, SE, MI, vascular death	132	197	0.66 (0.53, 0.83)	< 0.00036
All Cause death	111	140	0.79 (0.62, 1.02)	0.068

Interestingly, and not surprisingly, the effect of apixaban compared to aspirin in AVERROES was primarily on ischemic stroke. Thus, although apixaban does not seem clearly superior to warfarin in its effect on ischemic stroke in ARISTOTLE, both drugs are effective, as the comparison with aspirin shows clearly for apixaban, and as is known from previous warfarin studies.

Table 8

	Apixaban N=2807	Aspirin N=2791	HR
FIRST EVENT			
Ischemic/unspecified stroke	38	94	
Hemorrhagic stroke	5	6	
SE	2	11	
MI	21	23	
Vascular death	84	96	0.87 (0.65, 1.17)
Non-vascular death	27	44	0.62 (0.38, 1.00)

Obviously, the striking stroke effect is not surprising, but the effect on non-vascular death would be hard to explain.

Bleeding in AVERROES was more frequent on apixaban but fatal and intracranial bleeding rates were similar on the two treatments.

Table 9

	Apixaban	Aspirin	HR	p
Major	45	29	1.54 (0.96, 2.45)	0.07
Fatal	5	5	0.99	
Intracranial	11	11	0.99	

III. Conclusion

Apixaban shows clear effectiveness in decreasing rates of stroke or systemic embolism compared to warfarin in an ITT analysis (Table 1), with effect most prominent (Table 2) on hemorrhagic stroke and on hemorrhagic stroke plus ischemic stroke with hemorrhagic transformation. The advantage in pure ischemic stroke is not clear. Effectiveness is shown both for ITT analysis and on-therapy or on-therapy plus 2-7 days (Table 3). Major bleeding events were significantly less frequent with apixaban (Table 4). The nominally significant mortality advantage of apixaban should be noted in labeling. The clear advantage of apixaban on hemorrhagic stroke is a plausible driver of the mortality effect. It is of interest that all three warfarin alternatives have had their largest advantage (rivaroxaban, apixaban) over warfarin on the hemorrhagic stroke endpoint with lesser, but real advantages (dabigatran), or no clear advantage on ischemic stroke, where warfarin is very effective, AVERROES shows clearly that apixaban has a very substantial effect on this endpoint compared to aspirin.

Apixaban should be approved for reducing the rate of stroke on systemic embolism in patients with nonvalvular AF. Labeling should include a warning (Boxed Warning and Section 5 warning) of the need for particular care when apixaban is discontinued and of increased bleeding risk with a wide range of other drugs (aspirin and other anti-platelet drugs, SSRI/SNRI, NSAIDs, other anticoagulants. Like rivaroxaban and dabigatran there is no specific reversal agent for apixaban, although activated charcoal can block the prolonged absorption of apixaban and speed elimination.

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/s/

ROBERT TEMPLE
12/28/2012