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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.

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