



NDA 202155/S-002

SUPPLEMENT APPROVAL

Bristol-Myers Squibb
ATTENTION: Linda Gambone, Ph.D.
Associate Director, Global Regulatory Sciences
P.O. Box 4000
Princeton, NJ 08543-4000

Dear Dr. Gambone:

Please refer to your Supplemental New Drug Application (sNDA) dated April 29, 2013, received April 29, 2013, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Eliquis (apixaban) 2.5 and 5 mg Tablets.

This Prior Approval supplemental new drug application provides verbiage to better differentiate temporary interruption vs. discontinuation, new information and dosing recommendations for patient with end stage renal disease, and to include data from a drug-drug interaction study with prasugrel. The agreed upon changes to the Full Prescribing Information (FPI) language are as follows:

- The title of subsection 2.3 was changed to “**Temporary Interruption for Surgery and Other Interventions**”
- The subsection of **DOSAGE AND ADMINISTRATION, 2.7 Renal Impairment**, was changed from:

“The dosing adjustment for moderate renal impairment is described above [*see Dosage and Administration (2.2)*]. No data inform use in patients with creatinine clearance <15 mL/min or on dialysis.”

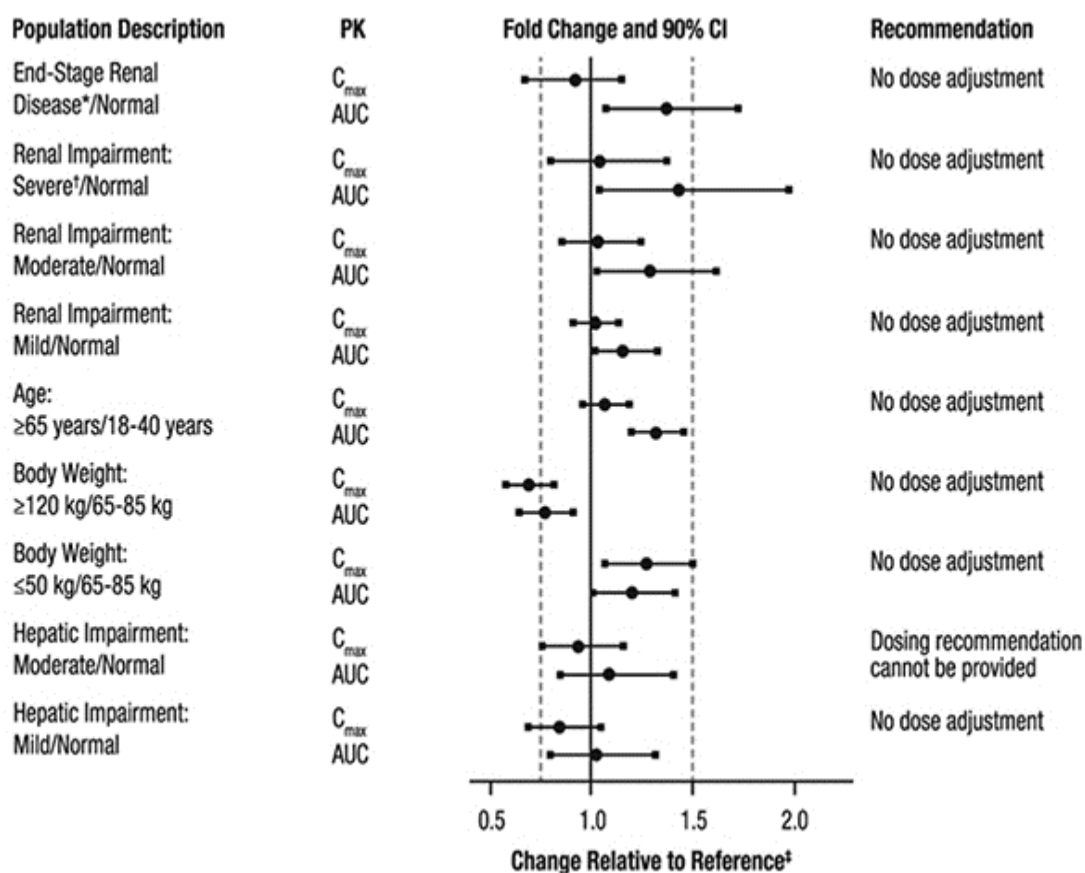
To

“The dosing adjustment for moderate renal impairment is described above [*see Dosage and Administration (2.2)*]. The recommended dose for patients with end-stage renal disease (ESRD) maintained on hemodialysis is 5 mg twice daily. Reduce dose to 2.5 mg twice daily if one of the following patient characteristics (age \geq 80 years or body weight \leq 60 kg) is present [*see Use in Specific Population (8.6) and Clinical Pharmacology (12.3)*].”

- A new subsection within **USE IN SPECIFIC POPULATIONS** was added. This new subsection, **8.6 End-Stage Renal Disease Patients Maintained with Hemodialysis**, reads:

“Patients with ESRD with or without hemodialysis were not studied in clinical efficacy and safety studies with ELIQUIS; therefore, the dosing recommendation is based on pharmacokinetic and pharmacodynamic (anti-Factor Xa activity) data in subjects with ESRD maintained on dialysis. The recommended dose for ESRD patients maintained with hemodialysis is 5 mg orally twice daily. For ESRD patients maintained with hemodialysis with one of the following patient characteristics, age ≥ 80 years or body weight ≤ 60 kg, reduce dose to 2.5 mg twice daily [see *Dosage and Administration* (2.7), *Clinical Pharmacology* (12.2, 12.3)].”

- In subsection 12.3, **Pharmacokinetics**, Figure 3, “Effect of Specific Populations on the Pharmacokinetics of Apixaban” was replaced with the below:



* ESRD subjects maintained with chronic and stable hemodialysis; Reported PK findings are following single dose of apixaban post hemodialysis.

† Creatinine clearance 15 to 29 mL/min.

‡ Dashed vertical lines illustrate pharmacokinetic changes that were used to inform dosing recommendations.

- There were also a few minor editorial and formatting changes made to throughout the FPI.
- The HIGHLIGHTS and Table of Contents were amended to reflect these changes to the FPI.

APPROVAL & LABELING

We have completed our review of this supplemental application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed, agreed-upon labeling text.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit the content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format using the FDA automated drug registration and listing system (eLIST), as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Content of labeling must be identical to the enclosed labeling (text for the package insert and Medication Guide), with the addition of any labeling changes in pending “Changes Being Effected” (CBE) supplements, as well as annual reportable changes not included in the enclosed labeling.

Information on submitting SPL files using eList may be found in the guidance for industry titled “SPL Standard for Content of Labeling Technical Qs and As at <http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>

The SPL will be accessible from publicly available labeling repositories.

Also within 14 days, amend all pending supplemental applications that includes labeling changes for this NDA, including CBE supplements for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 314.50(1)(1)(i)] in MS Word format, that includes the changes approved in this supplemental application, as well as annual reportable changes and annotate each change. To facilitate review of your submission, provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of these criteria apply to your application, you are exempt from this requirement.

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please contact:

Alison Blaus, RAC
Regulatory Project Manager
(301) 796-1138

Sincerely,

{See appended electronic signature page}

Mary Ross Southworth, Pharm.D.
Deputy Director for Safety
Division of Cardiovascular and Renal Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE:
Content of Labeling

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ALISON L BLAUS
01/30/2014

MARY R SOUTHWORTH
01/30/2014