DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 202439-S015

SUPPLEMENT APPROVAL

Janssen Research & Development LLC
Attention: Purve Patel, RPh
Director, Global Regulatory Affairs
920 Route 202 South
Raritan, NJ 08869

Dear Ms. Patel:

Please refer to your Supplemental New Drug Application (sNDA) dated 11 December 2014, received 11 December 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for XARELTO (rivaroxaban) Tablets.

We acknowledge receipt of your amendments dated 27 March, 1 May, and 30 July 2015.

This Prior Approval supplemental new drug application proposes changes to labeling which is aimed to harmonize the presentation of safety and efficacy data in the labels for all recently approved non-vitamin K-dependent oral anticoagulants (NOACs). The agreed upon changes are as follows:

1. In Section 6, **ADVERSE REACTIONS**, the presentation of the bleeding events was amended to appear as follows. To eliminate redundancy, some information that once appeared prior to the bleeding table (and in the table) was also deleted:

Table 1: Bleeding Events in ROCKET AF*- On Treatment Plus 2 Days

Parameter	XARELTO N = 7111 n (%/year)	Warfarin N = 7125 n (%/year)	XARELTO vs. Warfarin HR (95% CI)
Major Bleeding[†]	395 (3.6)	386 (3.5)	1.04 (0.90, 1.20)
Intracranial Hemorrhage (ICH)[‡]	55 (0.5)	84 (0.7)	0.67 (0.47, 0.93)
Hemorrhagic Stroke[§]	36 (0.3)	58 (0.5)	0.63 (0.42, 0.96)
Other ICH	19 (0.2)	26 (0.2)	0.74 (0.41, 1.34)
Gastrointestinal (GI)[¶]	221 (2.0)	140 (1.2)	1.61 (1.30, 1.99)
Fatal Bleeding[#]	27 (0.2)	55 (0.5)	0.50 (0.31, 0.79)
ICH	24 (0.2)	42 (0.4)	0.58 (0.35, 0.96)
Non-intracranial	3 (0.0)	13 (0.1)	0.23 (0.07, 0.82)

Abbreviations: HR = Hazard Ratio, CI = Confidence interval, CRNM = Clinically Relevant Non-Major.

* Major bleeding events within each subcategory were counted once per patient, but patients may have contributed events to multiple subcategories. These events occurred during treatment or within 2 days of stopping treatment.

† Defined as clinically overt bleeding associated with a decrease in hemoglobin of ≥2 g/dL, a transfusion of ≥2 units of packed red blood cells or whole blood, bleeding at a critical site, or with a fatal outcome.

‡ Intracranial bleeding events included intraparenchymal, intraventricular, subdural, subarachnoid and/or epidural hematoma.

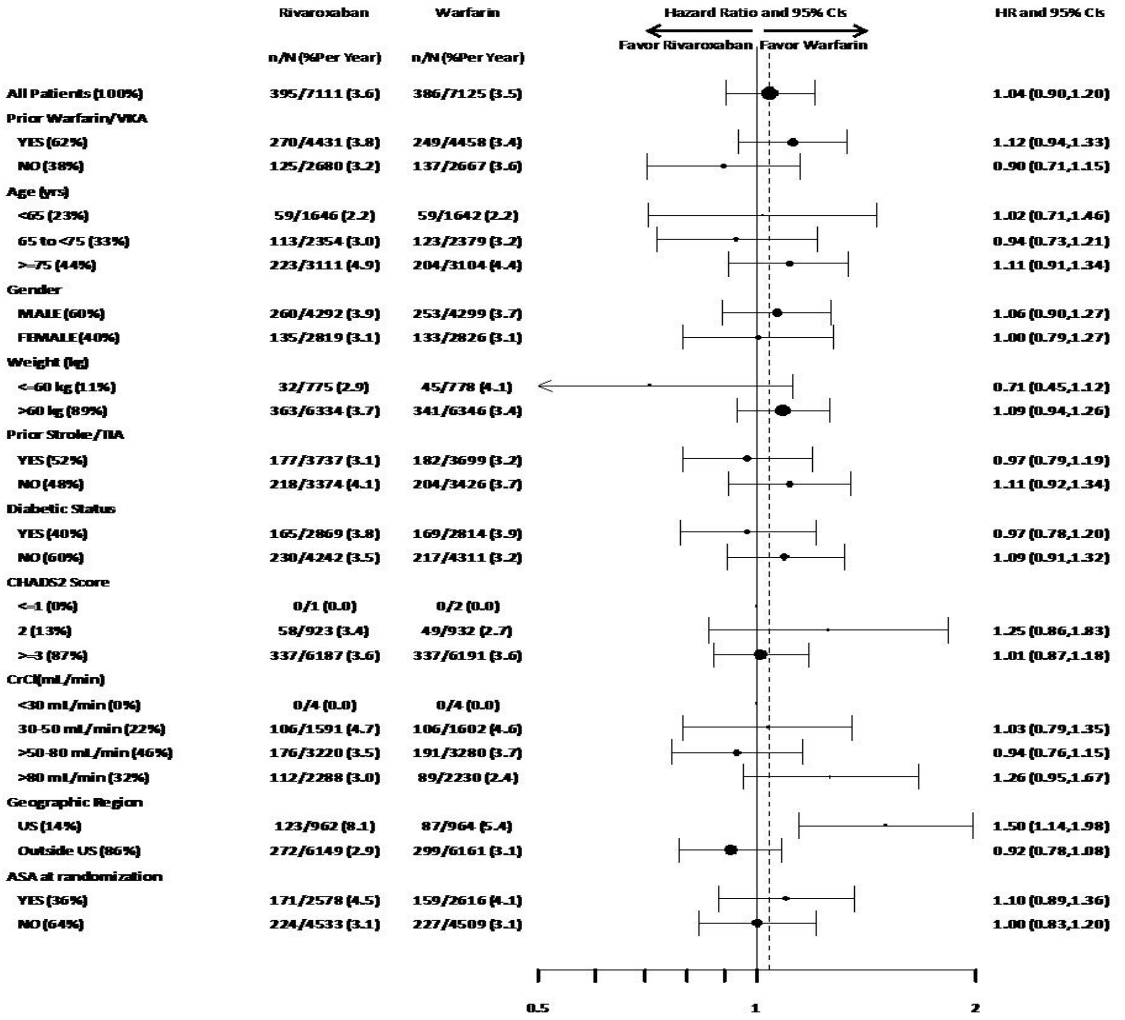
§ Hemorrhagic stroke in this table specifically refers to non-traumatic intraparenchymal and/or intraventricular hematoma in patients on treatment plus 2 days.

¶ Gastrointestinal bleeding events included upper GI, lower GI, and rectal bleeding.

Fatal bleeding is adjudicated death with the primary cause of death from bleeding.

2. A forest plot was added to Section 6. The population used was On-Treatment plus 2 days:

Figure 1: Risk of Major Bleeding Events by Baseline Characteristics in ROCKET AF – On Treatment Plus 2 Days



3. The following standard cautionary paragraph was included at the bottom of the forest plot:

> Note: The figure above presents effects in various subgroups all of which are baseline characteristics and all of which were pre-specified (diabetic status was not pre-specified in the subgroup, but was a criterion for the CHADS2 score). The 95% confidence limits that are shown do not take into account how many comparisons were made, nor do they reflect the effect of a particular factor after adjustment for all other factors. Apparent homogeneity or heterogeneity among groups should not be over-interpreted.

4. In Section 14, **CLINICAL STUDIES**, the forest plot was amended to include the same subgroups as the plot in Section 6 and also to present the data in an identical way as Section 6. The population used to generate the forest plot, however, is different than that in Section 6. The

population used in Section 14 was Intent-to-Treat (ITT).

5. In Section 12.3, **CLINICAL PHARMACOLOGY**, Pharmacokinetics, the effect of certain drugs on the pharmacokinetics of a NOAC were depicted in a plot rather than describing the study data in paragraph form. To eliminate redundancy, the descriptions of the studies included in the plot were removed.

6. Other minor editorial changes were also made throughout the label.

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(l)] 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), 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(l)(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).

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
Senior 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
09/09/2015

MARY R SOUTHWORTH
09/10/2015