DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 206316-S002

SUPPLEMENT APPROVAL

Daiichi-Sankyo Inc.
Attention: Doreen Morgan, PharmD, MS
Executive Director, Regulatory Affairs
399 Thornall Street
Edison, NJ 08837

Dear Dr. Morgan:

Please refer to your Supplemental New Drug Application (sNDA) dated 14 May 2015, received 14 May 2015, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for SAVAYSA (edoxaban tosylate) 15, 30, and 60 mg Tablets.

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 6.1: Adjudicated Bleeding Events for NVAF Patients with CrCL ≤ 95 mL/min*

Event[a]	SAVAYSA 60 mg[b] N = 5417 n (%/year)	Warfarin N = 5485 n (%/year)	SAVAYSA 60 mg vs. Warfarin HR (95% CI)
Major Bleeding[c]	357 (3.1)	431 (3.7)	0.84 (0.73, 0.97)
Intracranial Hemorrhage (ICH)[d]	53 (0.5)	122 (1.0)	0.44 (0.32, 0.61)
Hemorrhagic Stroke	33 (0.3)	69 (0.6)	0.49 (0.32, 0.74)
Other ICH	20 (0.2)	55 (0.5)	0.37 (0.22, 0.62)
Gastrointestinal[e]	205 (1.8)	150 (1.3)	1.40 (1.13, 1.73)
Fatal Bleeding[f]	21 (0.2)	42 (0.4)	0.51 (0.30, 0.86)
ICH	19 (0.2)	36 (0.3)	0.54 (0.31, 0.94)
Non-intracranial	2 (<0.1)	6 (<0.1)	----

Abbreviations: HR = Hazard Ratio versus Warfarin, CI = Confidence Interval, n = number of patients with events, N = number of patients in Safety population,

* The on treatment period is during treatment or within 2 days of stopping study treatment. The difference in hemorrhagic stroke rate from Table 14.1 is because Table 14.1 includes events occurring during treatment or within 3 days of stopping study treatment and this table only includes patients with CrCL≤95 mL/min.
[a] A subject can be included in multiple sub-categories if he/she had an event for those categories.
[b] Includes all patients with CrCL ≤ 95 mL/min randomized to receive 60 mg once daily, including those who were dose-reduced to 30 mg once daily because of prespecified baseline conditions.
[c] A Major Bleeding event (the study primary safety endpoint) was defined as clinically overt bleeding that met one of the following criteria: fatal bleeding; symptomatic bleeding in a critical site such as retroperitoneal, intracranial, intraocular, intraspinal, intra-articular, pericardial, or intramuscular with compartment syndrome; a clinically overt bleeding event that caused a fall in hemoglobin of at least 2.0 g/dL (or a fall in hematocrit of at least 6.0% in the absence of hemoglobin data), when adjusted for transfusions (1 unit of transfusion = 1.0 g/dL drop in hemoglobin).
[d] ICH includes primary hemorrhagic stroke, subarachnoid hemorrhage, epidural/subdural hemorrhage, and ischemic stroke with major hemorrhagic conversion.
[e] Gastrointestinal (GI) bleeds include bleeding from upper and lower GI tract. Lower GI tract bleeding includes rectal bleeds.
[f] Fatal bleed is a bleeding event during the on treatment period and adjudicated as leading directly to death within 7 days.

2. In Section 12.3, **CLINICAL PHARMACOLOGY**, Pharmacokinetics, Figure 12.1 (Summary of Drug Interaction Study Results) was reformatted and amended to present AUC instead of AUCtau.

3. 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