

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

206316Orig1Orig2s000

Trade Name: SAVAYSA 15, 30, and 60 mg Tablets.

Generic Name: edoxaban tosylate

Sponsor: Daiichi-Sankyo Inc.

Approval Date: January 8, 2015

Indication: NDA 206316/Original 1 - Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation

NDA 206316/Original 2 - Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) following 5-10 days of initial therapy with a parenteral anticoagulant

CENTER FOR DRUG EVALUATION AND RESEARCH

206316Orig1Orig2s000

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**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

206316Orig1Orig2s000

APPROVAL LETTER



NDA 206316/Original 1

NDA 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 New Drug Application (NDA) dated January 8, 2014, received January 8, 2014, submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for SAVAYSA (edoxaban tosylate) 15, 30, and 60 mg Tablets.

We acknowledge receipt of your amendments dated January 14, 21, 31, February 3, 10, 24, 28, March 6 (two), 10 (two), 13, 18, 21, 27, 28, April 3, 10, 18, 23, 24, 30, May 8, 21, 27, June 16, 19, 24, July 7, 10, 24, August 1, 13, 18, 20, 25, September 8, 11, 22, October 29, December 5 and 22, 2014.

NDA 206316 provides for the use of SAVAYSA Tablets for the following indications which, for administrative purposes, we have designated as follows:

- NDA 206316/Original 1 - Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation
- NDA 206316/Original 2 - Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) following 5-10 days of initial therapy with a parenteral anticoagulant

- [REDACTED] (b) (4)

The subject of this action letter is NDA 206316/Original 1. A separate action letter will be issued for NDA 206316/Original 2 [REDACTED] (b) (4).

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

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(I)] 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). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

The SPL will be accessible via publicly available labeling repositories.

CARTON AND IMMEDIATE-CONTAINER LABELS

Submit final printed carton and container labels that are identical to the enclosed carton and immediate container labels, as soon as they are available, but no more than 30 days after they are printed. Please submit these labels electronically according to the guidance for industry titled “Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications (June 2008).” Alternatively, you may submit 12 paper copies, with 6 of the copies individually mounted on heavy-weight paper or similar material. For administrative purposes, designate this submission “**Final Printed Carton and Container Labels for approved NDA 206316.**” Approval of this submission by FDA is not required before the labeling is used.

Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

MARKET PACKAGE

Please submit one market package of the drug product when it is available.

If sending via USPS, please send to:

Alison Blaus
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 4158
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

If sending via any carrier other than USPS
(e.g., UPS, DHL), please send to:

Alison Blaus
Food and Drug Administration
Center for Drug Evaluation and Research
White Oak Building 22, Room: 4158
10903 New Hampshire Avenue
Silver Spring, Maryland 20903

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.

We are waiving the pediatric study requirement for this application because necessary studies are impossible or highly impracticable because the disease is rare in children.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

2852-3 Development of a discriminating and canonical dissolution method

The timetable you submitted on December 5, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	2/2015
Study/Trial Completion:	3/2016
Final Report Submission:	4/2016

2852-4 Setting of dissolution acceptance criterion based on data from at least 12 commercial batches.

The timetable you submitted on December 5, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission:	2/2015
Study/Trial Completion:	3/2016
Final Report Submission:	4/2016

Submit clinical protocols to your IND 77254 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol**,” “**Postmarketing Commitment Final Report**,” or “**Postmarketing Commitment Correspondence**.”

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705-1266

As required under 21 CFR 314.81(b)(3)(i), you must submit final promotional materials, and the package insert, at the time of initial dissemination or publication, accompanied by a Form FDA 2253. Form FDA 2253 is available at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf>. Information and Instructions for completing the form can be found at

<http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf>. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see <http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm>.

REPORTING REQUIREMENTS

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

MEDWATCH-TO-MANUFACTURER PROGRAM

The MedWatch-to-Manufacturer Program provides manufacturers with copies of serious adverse event reports that are received directly by the FDA. New molecular entities and important new biologics qualify for inclusion for three years after approval. Your firm is eligible to receive copies of reports for this product. To participate in the program, please see the enrollment instructions and program description details at <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm166910.htm>.

POST APPROVAL FEEDBACK MEETING

New molecular entities and new biologics qualify for a post approval feedback meeting. Such meetings are used to discuss the quality of the application and to evaluate the communication process during drug development and marketing application review. The purpose is to learn from successful aspects of the review process and to identify areas that could benefit from improvement. If you would like to have such a meeting with us, call the Regulatory Project Manager for this application.

PDUFA V APPLICANT INTERVIEW

FDA has contracted with Eastern Research Group, Inc. (ERG) to conduct an independent interim and final assessment of the Program for Enhanced Review Transparency and Communication for NME NDAs and Original BLAs under PDUFA V ('the Program'). The PDUFA V Commitment Letter states that these assessments will include interviews with applicants following FDA action on applications reviewed in the Program. For this purpose, first-cycle actions include approvals, complete responses, and withdrawals after filing. The purpose of the interview is to better understand applicant experiences with the Program and its ability to improve transparency and communication during FDA review.

ERG will contact you to schedule a PDUFA V applicant interview and provide specifics about the interview process. Your responses during the interview will be confidential with respect to the FDA review team. ERG has signed a non-disclosure agreement and will not disclose any identifying information to anyone outside their project team. They will report only anonymized results and findings in the interim and final assessments. Members of the FDA review team will be interviewed by ERG separately. While your participation in the interview is voluntary, your feedback will be helpful to these assessments.

If you have any questions, please call

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

Sincerely,

{See appended electronic signature page}

Robert Temple, MD
Deputy Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosures:

Content of Labeling
Carton and Container Labeling

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

/s/

ROBERT TEMPLE
01/08/2015



NDA 206316/Original 2

NDA APPROVAL

Daiichi Sankyo, Inc.
Attention: Doreen V. Morgan, PharmD, MS
Executive Director, Regulatory Affairs
399 Thornall Street, 10th Floor
Edison, NJ 08837

Dear Dr. Morgan:

Please refer to your New Drug Application (NDA) dated January 8, 2014, received January 8, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act (FDCA) for SAVAYSA™ (edoxaban tosylate) 15, 30, and 60 mg Tablets.

We acknowledge receipt of your amendments dated January 14, 21, and 31; February 3, 10, and 24, and 28; March 6 (2), 10 (2), 13, 18, 21, 27, and 28; April 3, 10, 18, 23, 24, and 30; May 8, 21, and 27; June 16, 19, and 24; July 7, 10, and 24; August 1, 13, 18, 20, and 25; September 8, 11, and 22; October 29; and December 5 and 22, 2014.

NDA 206316 provides for the use of SAVAYSA (edoxaban tosylate) Tablets for the following indications which, for administrative purposes, we have designated as follows:

- NDA 206316/Original 1 - Reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation
- NDA 206316/Original 2 - Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) following 5-10 days of initial therapy with a parenteral anticoagulant
- [REDACTED] (b) (4)

NDA 206316/Original 1 was reviewed by the Division of Cardiovascular and Renal Products and NDA 206316/Originals 2 [REDACTED] (b) (4) were reviewed by the Division of Hematology Products.

The subject of this action letter is NDA 206316/Original 2. A separate action letter will be issued for NDA 206316/Originals 1 [REDACTED] (b) (4)

We have completed our review of this 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 and Medication Guide). Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*, available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf>.

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Alice Tu
Food and Drug Administration
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White Oak Building 22, Room: 4325
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

If sending via any carrier other than USPS
(e.g., UPS, DHL), please send to:

Alice Tu
Food and Drug Administration
Center for Drug Evaluation and
Research
White Oak Building 22, Room: 4325
10903 New Hampshire Avenue
Silver Spring, Maryland 20903

ADVISORY COMMITTEE

Your application for SAVAYSA for the treatment of deep vein thrombosis and pulmonary embolism was not referred to an FDA advisory committee because this drug is not the first in its class.

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.

We are deferring submission of your pediatric studies until June 30, 2022, because this product is ready for approval for use in adults and the pediatric studies have not been completed.

Your deferred pediatric studies required under section 505B(a) of the (FDCA) are required postmarketing studies. The status of these postmarketing studies must be reported annually according to 21 CFR 314.81 and section 505B(a)(3)(B) of the FDCA. These required studies are listed below.

PMR 2852-1: Perform, complete and submit the full study report for a single-dose study of pharmacokinetics and pharmacodynamics (PK/PD) of edoxaban in pediatric patients at risk for venous thromboembolism (VTE), requiring anticoagulation or recently completing standard of care anticoagulation in accordance with your October 31, 2013 agreed upon Initial Pediatric Study Plan (iPSP).

Final Protocol Submission:	Completed 2/19/2014
Study Completion:	6/30/2017
Final Report Submission:	12/31/2017

PMR 2852-2: Perform, complete and submit the full study report for a phase 3 multicenter, randomized, active control study of edoxaban in pediatric patients with documented venous thromboembolism in accordance with your October 31, 2013 agreed upon Initial Pediatric Study Plan (iPSP).

Final Protocol Submission: 12/14/2016
Study/Trial Completion: 12/31/2021
Final Report Submission: 6/30/2022

Submit the protocol(s) to your IND 063266, with a cross-reference letter to this NDA.

Reports of these required pediatric postmarketing studies must be submitted as a new drug application (NDA) or as a supplement to your approved NDA with the proposed labeling changes you believe are warranted based on the data derived from these studies. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING COMMITMENTS NOT SUBJECT TO THE REPORTING REQUIREMENTS UNDER SECTION 506B

We remind you of your postmarketing commitments:

PMC 2852-3 Development of a discriminating and canonical dissolution method

The timetable you submitted on December 5, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 2/2015
Study Completion: 3/2016
Final Report Submission: 4/2016

PMC 2852-4 Setting of dissolution acceptance criterion based on data from at least 12 commercial batches.

The timetable you submitted on December 5, 2014, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 2/2015
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Submit clinical protocols to your IND 063266 for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all postmarketing final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii) you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies/trials, number of patients entered into each study/trial. All submissions, including supplements, relating to these postmarketing commitments should be prominently labeled “**Postmarketing Commitment Protocol**,” “**Postmarketing Commitment Final Report**,” or “**Postmarketing Commitment Correspondence**.”

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If you have any questions, call Janet G. Higgins, Regulatory Project Manager, at (240) 402-0330.

Sincerely,

{See appended electronic signature page}

Richard Pazdur, MD
Director
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure(s):
Content of Labeling
Carton and Container Labeling

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

/s/

RICHARD PAZDUR
01/08/2015