Cross-Discipline Team Leader Review

Date	09/22/23
From	Virginia E. Kwitkowski, MS, ACNP-BC
Subject	Cross-Discipline Team Leader Review
NDA/BLA # and Supplement#	sNDA 206316 S-019
Applicant	Daiichi Sankyo, Inc.
Date of Submission	12/19/2022
PDUFA Goal Date	10/19/2023
Proprietary Name	SAVAYSA
Established or Proper Name	Edoxaban
Dosage Form(s)	Tablets, for oral use
Applicant Proposed Indication(s)/Population(s)	No change
Applicant Proposed Dosing Regimen(s)	n/a
Recommendation on Regulatory Action	*Approval*
Recommended Indication(s)/Population(s) (if applicable)	*n/a*
Recommended Dosing Regimen(s) (if applicable)	*n/a*

1. Benefit-Risk Assessment

Table 1 Benefit Risk Integrated Assessment

Benefit-Risk Integrated Assessment
Pediatric venous thromboembolism (VTE) is an uncommon but serious and life-threatening condition with associated morbidity and mortality. Presence of a central venous catheter, admission to intensive care units, and conditions leading to a hypercoagulable state are risk factors for development of pediatric VTE. Dalteparin, Pradaxa, and Xarelto are the only anticoagulant products with a US-FDA-approved pediatric indication. Dalteparin, a low molecular weight heparin, is indicated for the treatment of symptomatic venous thromboembolism (VTE) to reduce the recurrence in pediatric patients 1 month of age and older. Pradaxa (dabigatran oral pellets), a direct thrombin inhibitor, is indicated for the treatment of VTE in pediatric patients aged 3 months to less than 12 years of age who have been previously treated with a parenteral anticoagulant for at least 5 days and to reduce the risk of recurrence of VTE in pediatric patients aged 3 months to less than 12 years of age who have been previously treated. Pradaxa (dabigatran capsules) are indicated for the treatment of VTE in pediatric patients 8 years to less than 18 years of age who have been treated with a parenteral anticoagulant for at least 5 days and to reduce the risk of recurrence of VTE in pediatric patients 8 to less than 18 years of age who have been previously treated. Xarelto (rivaroxaban tablets and for oral suspension), a factor Xa inhibitor, is indicated for the treatment of VTE and reduction in the risk of recurrent VTE in pediatric patients from birth to less than 18 years and for thromboprophylaxis in pediatric patients 2 years and older with congenital heart disease after the Fontan procedure. Unfractionated heparin may be considered to have an implied indication, though the indication statement does not specify pediatric patients, the dosage and administration subsection of the USPI has specific pediatric dosage recommendations. The main advantages of DOACs over SOC therapies are the fixed dose administration without the need for monitoring, the oral formulation availability and the presence of a specific targeted antidote. It is important to note that DOACs have been less effective in the treatment of patients with prosthetic heart valves and in patients with antiphospholipid antibody syndrome. The main common adverse reaction among all anticoagulants is the risk of bleeding, which can result in life-threatening major bleeding in ~2-3% of patients. This application is supported by the results of a randomized, open-label, multicenter, actively controlled trial to evaluate the pharmacokinetics

and pharmacodynamics of edoxaban and to compare the efficacy and safety of edoxaban with standard-of-care anticoagulant therapy in pediatric patients from birth to less than 18 years of age with confirmed venous thromboembolism. The primary study objective was to demonstrate the noninferiority of edoxaban to standard-of-care (including low-molecular weight heparin, vitamin K antagonist, or synthetic pentasaccharide Xa inhibitors) in the treatment and secondary prevention of VTE in pediatric subjects with regard to the composite efficacy endpoint (i.e., symptomatic recurrent VTE, death as a result of VTE, and no change or extension of thrombotic burden) during the first 3-month treatment period (for cohort 5, the intended duration of treatment is 6 to 12 weeks).

The Applicant provided no evidence of effectiveness as the non-inferiority trial for Savaysa (edoxaban) in pediatric patients did not achieve its primary endpoint. The primary efficacy endpoint was the composite endpoint consisting of symptomatic recurrent VTE, death as a result of VTE, and no change or extension of thrombotic burden during the Main Treatment Period. The benefit:risk assessment is negative.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• The annual incidence of VTE in children is reported as 0.07 - 0.14 per 10,000 children, with higher rates in neonates and adolescents. • The rate of VTE in hospitalized children has increased by 70% over the past 10-20 years. • The most significant VTE risk factors are the presence of a central venous catheter, admission to an intensive care unit and conditions that lead to a hypercoagulable state. • VTE is serious life-threatening medical condition with significant morbidity and mortality in pediatric patients, such as pulmonary embolism, post thrombotic syndrome and an untreated VTE-related mortality rate of ~3%.	VTE is an uncommon but serious disease in children. If untreated, VTE can lead to serious and life-threatening outcome, with significant morbidity and mortality.
Current Treatment Options	• Dalteparin, a low molecular weight heparin, is indicated for the treatment of symptomatic venous thromboembolism (VTE) to reduce the recurrence in pediatric patients 1 month of age and older. • Pradaxa (dabigatran oral pellets), a direct thrombin inhibitor, is indicated for the treatment of VTE in pediatric patients aged 3 months to less than 12 years of age who have been previously treated with a parenteral anticoagulant for at least 5 days and to reduce the	Specifically, there is a need for oral anticoagulant therapies in pediatric patients that require minimal to no monitoring and have a dependable reversal agent. DOACs offer a potentially significant new therapy for VTE in pediatric patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	risk of recurrence of VTE in pediatric patients aged 3 months to less than 12 years of age who have been previously treated. Pradaxa (dabigatran capsules) are indicated for the treatment of VTE in pediatric patients 8 years to less than 18 years of age who have been treated with a parenteral anticoagulant for at least 5 days and to reduce the risk of recurrence of VTE in pediatric patients 8 to less than 18 years of age who have been previously treated. • Xarelto (rivaroxaban tablets and for oral suspension), a factor Xa inhibitor, is indicated for the treatment of VTE and reduction in the risk of recurrent VTE in pediatric patients from birth to less than 18 years and for thromboprophylaxis in pediatric patients 2 years and older with congenital heart disease after the Fontan procedure. • Other standard of care (SOC) treatment options, most of which are used in an off-label fashion, include heparin products, vitamin K antagonists, fondaparinux and parenteral thrombin inhibitors. • Unfractionated heparin may be considered to have an implied indication because the Dosage and Administration section of the USPI contains pediatric dosing recommendations. • The main advantages of DOACs over SOC therapies are the fixed dose administration without the need for monitoring, the oral formulation availability and the presence of a specific targeted antidote. • There are no FDA-approved antidotes/reversal agents for DOACs for pediatric patients.	
Benefit	• The Edoxaban Hokusai VTE PEDIATRICS Study, a phase 3, randomized, open-label, actively controlled trial did not demonstrate non-inferiority to the standard-of—care arm with regards to the primary composite endpoint of “symptomatic recurrent VTE, death as a result of VTE, and no change or extension of thrombotic burden”. Therefore, efficacy was not demonstrated.	The trial did not demonstrate effectiveness for edoxaban in the treatment of VTE in pediatric patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• Safety results were comparable between the edoxaban and SOC arms with regards to the number of patients with an adjudicated confirmed major and clinically relevant nonmajor bleed during the Main Treatment Period and On-Treatment (HR 0.60 [95% CI; 0.139 to 2.597]). At least 1 adjudicated confirmed major and CRNM bleeding event occurred in 3 (2.1%) of patients in the edoxaban group and 5 (3.5%) of patients in the SOC group. • Treatment-emergent adverse events occurred in 71% of patients on the edoxaban arm and 67% of those on the SOC arm. The most common (≥4%) TEAEs on the edoxaban arm included headache, vomiting, nasopharyngitis, cough, dizziness, rash, and urinary tract infection.	No novel pediatric safety issues were identified during this trial. Safety cannot be demonstrated without efficacy.

2. Background

Savaysa (edoxaban tablets for oral use) is a factor Xa inhibitor that was initially approved on 01/08/2015 for the following indications:

- To reduce the risk of stroke and systemic embolism (SE) in patients with nonvalvular atrial fibrillation (NVAF)
- For the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) following 5 to 10 days of initial therapy with a parenteral anticoagulant

The recommended dose for both indications is 60 mg once daily (with dose reductions for renal impairment and (b) (4)). Additionally, for treatment of DVT/PE, dose-reduction is recommended for patients with concomitant use of certain P-gp inhibitors.

With this approval, a postmarketing requirement was issued based upon the Pediatric Research Equity Act (PREA). PMR 2852-2 required the applicant "to 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."

The original protocol was submitted to DNH under IND 63266 on 08/15/2016.

Daiichi Sankyo, Inc. submitted this efficacy supplement which includes the clinical study report for study DU176B-D-U312, "A Phase 3, open-label, randomized, multi-center, controlled trial to evaluate the pharmacokinetics and pharmacodynamics of edoxaban and to compare the efficacy and safety of edoxaban with standard of care anticoagulant therapy in pediatric patients from birth to less than 18 years of age with confirmed venous thromboembolism (VTE)".

Daiichi Sankyo, Inc. proposes changes to the USPI based on the findings of this completed study. (b) (4) the only changes to the USPI are in 'Section 8.4 Pediatric Use'.

The therapeutic context for the treatment of VTE/PE in pediatric patients includes:
Approved Therapies:

- Pradaxa (dabigatran) oral pellets (Indications: Treatment of venous thromboembolic event (VTE) in pediatric patients aged 3 months to less < 12 years of age who have been treated with a parenteral anticoagulant for at least 5 days AND To reduce the risk of recurrence of VTE in pediatric patients aged 3 months to < 12 years of age who have been previously treated.
- Fragmin (dalteparin) Injection (Indication: Treatment of symptomatic venous thromboembolism (VTE) to reduce the recurrence in pediatric patients 1 month of age and older.)
- Heparin sodium injection (Indication: prophylaxis and treatment of VTE and PE) [no pediatric indication, but implied due to pediatric dosing recommendations]
- Xarelto (rivaroxaban) tablets and 'for oral suspension' (treatment of VTE and reduction in risk of recurrent VTE in pediatric patients from birth to <18 years and for thromboprophylaxis in pediatric patients 2 years and older with congenital heart disease after the Fontan procedure). AndeXxa (coagulation factor Xa-recombinant inactivated-zhzo is an approved reversal agent for rivaroxaban.

Off-Label Use:

- Coumadin (warfarin) tablets
- Lovenox (enoxaparin) injection
- Arixtra(fondaparinux) injection
- Angiomax (bivalirudin) for injection

There remains unmet medical need for anticoagulants for pediatric patients. Heparin sodium requires venous access and therapeutic monitoring using aPTT (so is only feasibly used in an inpatient setting), carries the risk of heparin-induced thrombocytopenia, and has an unpredictable, age-dependent PK profile. Coumadin is an orally available drug but is limited by only being available as a tablet (not

helpful for children who cannot swallow tablets), requires PT and INR monitoring, has risk of bleeding, and has significant drug and food interactions. Xarelto is available as tablets and for oral suspension, so is helpful for young children who cannot swallow tablets. There remains a need for safe and effective oral anticoagulants in an appropriate pediatric formulations, with predictable pharmacokinetics which do not require significant therapeutic monitoring or dose adjustments.

Regulatory Background

This efficacy supplement is submitted to fulfill PREA PMRs issued on 01/08/2015 with the approval of Savaysa.
The PMRs issued were:

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

8/15/2016 Submission of pediatric study protocols (PMR2852-1 and PMR2852-2) under the iPSP as part of Post Marketing Requirements

2/19/2021 PMR/PMC milestones were revised for PMR 2852-1 due to difficulties with recruitment of study subjects.

2/19/2021 The Agency granted a pediatric deferral extension for the study completion to 09/2021 and the final report submission to 12/2021.

1/12/2023 The Agency granted a pediatric deferral extension for study completion of the Phase 3 trial to 12/2022 and final report submission date to 06/2023.

PMR 2852-1 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).
Final Report Submission: 03/2022 (submitted 01/28/2022)

PMR 2852-2, a phase 3 multicenter, randomized, active control study of edoxaban in pediatric patients with documented venous thromboembolism).
Study Completion: 12/2022 (revised date)
Final Report Submission: 6/2023 (submitted 12/19/2022)

(b) (4)

See the primary clinical/statistical review for further details on presubmission regulatory history.

See Table 2 for the clinical studies originally agreed upon for the PSP.

Table 2 Clinical Studies in Edoxaban Pediatric Development Program

Study Ref #	Short Title/ Study Design	Study Start (FPI)	Sample Size/ Population	Key Objectives	Endpoints
1	Relative Bioavailability/ Food Effects Study of an Edoxaban Pediatric Formulation (open-label, randomized, 3-way crossover)	June 2013	N=24; Healthy adult subjects	Characterize PK of edoxaban oral suspension, assess relative bioavailability vs oral tablet; assess food effects and palatability of peds formulation	PK, RBA, Food effects, palatability
2	Phase 1 Pediatric PK/PD Study (open-label, single dose, non-randomized)	June 2014	N=48; Pediatric patients at risk for VTE, requiring anticoagulation or recently completing standard of care anticoagulation	Evaluate PK/PD, safety /tolerability in pediatrics; assess palatability of peds formulation	PK, PD biomarkers, VAS for palatability
3	Phase 3 Pediatric VTE Study (international, multi-center, open-label, randomized, active-control)	December 2016	N=500; pediatric patients with documented VTE	Compare efficacy/safety of (LMW) Heparin or fondaparinux followed by edoxaban vs. SOC	composite of recurrent VTE, VTE-related death, and thrombotic burden

3. Product Quality

No new CMC information was submitted with this application. No new pediatric formulation will be approved because no pediatric indication is granted.

4. Nonclinical Pharmacology/Toxicology

- No new nonclinical information was submitted with this application.

5. Clinical Pharmacology

The Clinical Pharmacology primary reviewer is Harisudhan Thanukrishnan, PharmD and his Team Leader is Sudharshan Hariharan, PharmD. The clinical pharmacology review was archived on 09/14/23.

To support pediatric dosing, the Applicant developed edoxaban granules for oral suspension (60 mg). Patients younger than 12 years of age received edoxaban granules for oral suspension according to body weight, in the above Phase 1 study. The relative oral bioavailability of granules for oral suspension (10 mL of 6 mg/mL) versus tablets (2 x 30 mg) was assessed in healthy adult subjects (Study DU176b-AU154). The exposure (AUC_{last} and AUC_{inf}) was similar between both formulations but the Cmax of oral suspension was 13% lower than the tablets.

The Office of Clinical Pharmacology (OCP)/ Division of Cardiometabolic and Endocrine Pharmacology has reviewed the information contained in this supplement of NDA 206316. The Applicant has fulfilled PMR 2852-1 with completion of the single dose PK/PD study in pediatric patients. Based on this PK/PD study, the Applicant identified doses for pediatric patients across different age cohorts for evaluation in the efficacy trial. While selection of pediatric doses resulted in exposures in the range of adult exposures equivalent to 60 mg in patients with VTE, the simulated median steady-state AUC0-24 was approximately 18 to 27% lower compared to adult exposures. The current pediatric efficacy trial failed due to inadequate sample size, however, if the Applicant were to conduct another trial, the pediatric dosing could be refined further to match adult exposures even closely.

No PMRs or PMCs were recommended by the Clinical Pharmacology review team.

6. Clinical Microbiology

No clinical microbiology information was submitted with this application.

7. Clinical/Statistical- Efficacy

Two clinical studies were reviewed during this supplement.
The first pediatric study was DU176b-A-U157 which is titled "A Phase 1, Open-label, Single-dose, Non-randomized Study to Evaluate Pharmacokinetics (PK) and Pharmacodynamics (PD) of Edoxaban in Pediatric Patients" (n=66). No efficacy endpoints were included in this study and no new pediatric-specific safety issues were identified in the review of this study.

The pivotal pediatric study was DU176b-D-U312 which is titled "A Phase 3, Open-Label, Randomized, Multicenter, Controlled Trial to Evaluate the Pharmacokinetics and Pharmacodynamics of Edoxaban and to Compare the Efficacy and Safety of Edoxaban with Standard-of-Care Anticoagulant Therapy in Pediatric Subjects from Birth to Less Than 18 Years of Age with Confirmed Venous Thromboembolism (VTE)" (n=286).

Because the pivotal trial failed to establish the efficacy of Savaysa in pediatric patients, the main focus of the clinical and statistical reviews were to:

- Evaluate whether Daiichi Sankyo has successfully fulfilled the PMR requirements for PMR 2852-1 and 2852-2 under the Pediatric Research Equity Act for NDA 206316
- To update the Pediatric Use section of the USPI with a high-level summary of the trial
- To evaluate potential causes for the trial failure
- To review the safety data for possible novel pediatric risks associated with Savaysa treatment

This supplement provides for changes to the Savaysa USPI to reflect the findings from trial DU176B-D-U312. The primary efficacy endpoint was the composite endpoint (consisting of symptomatic recurrent VTE, death as a result of VTE, and no change or extension of thrombotic burden during the Main Treatment Period. The hazard ratio (HR) for the edoxaban group versus the SOC group was 1.01 (95% CI: 0.594 to 1.719). The upper bound of the 95% CI (1.719) was above the prespecified noninferiority margin of 1.5, and the noninferiority of edoxaban versus SOC was not confirmed. Therefore, as efficacy was not established, the benefit:risk assessment is negative. The application does not contain substantial evidence of effectiveness. No indication for pediatric patients was requested and none will be granted.

Refer to the primary clinical/statistical joint review for details of the trial results.

In summary:

- The review team concluded that PREA PMR 2852-1 was fulfilled by the Applicant.
- The review team concluded (with support from PerC) that PREA PMR 2852-2 was NOT fulfilled by the Applicant.
- The USPI section 8.4 Pediatric Use was updated to summarize the results of the Phase 3 pediatric trial.
- The clinical and statistical review team concluded that the only reason identified for trial failure was that the trial was underpowered. The Applicant had planned to conduct an interim analysis after approximately 50% of information was available to allow for adjustment of the number of subjects in the study (if necessary). This pediatric study aimed to observe a total of 68 events, with an expected event rate of 24%, and it initially had a sample size of 274. However, during the interim analysis, the Applicant observed 23 events among the 138 enrolled patients, resulting in an event rate of 16.7%. Based on this analysis, the sample size was recalculated to be 422, which would have led to approximately 68 events by the end of the study, assuming the observed event rate remained constant. Despite the recommendation from the interim analysis, the Applicant chose to disregard it and terminated the study at a sample size of 286. At that point, they had observed 57 events, with an event rate of 20%. Consequently, the resulting analysis yielded a wide 95% confidence interval of 1.01 (0.59, 1.72), with the upper bound exceeding the non-inferiority margin of 1.5. Based on these findings, the study seemed to be underpowered, meaning it did not have a sufficient sample size to assess the non-inferiority of edoxaban to SOC arm. This is in contrast to the adult study (DU176b-D-U305 (Hokusai VTE)), which was confirmed based on a hazard ratio of .89 (95% CI 0.70, 1.13), where the upper bound of the 95% confidence interval was below the threshold of 1.5.
- The safety data from the randomized trial were evaluated and no novel pediatric safety issues were identified.

No new PMRs or PMCs are recommended by the clinical or statistical team.

8. Safety

The safety data was analyzed to evaluate for novel safety issues with the pediatric population. The safety in pediatric patients appeared similar to that in adults.

Safety cannot be established until efficacy is established.

See the primary clinical/statistical review for details of the complete safety analysis.

9. Advisory Committee Meeting

This application was not presented to an advisory committee because no indication was sought.

10. Pediatrics

The two clinical trials submitted with this application were the subject of two PREA PMRS (2852-1, 2852-2).

This application was discussed with the PerC on 09/12/23. The Division asked PerC if they would support our recommendation to not fulfill PMR 2852-2 due to the failure of the Applicant to complete the trial as agreed upon in the PSP and the PMR which reads "Perform, complete, and submit…". The PerC agreed unanimously with the Division's conclusion that PMR 2852-2 was not fulfilled. The recommendation is to issue a letter stating that the PMR was not fulfilled.

There appear to be two options with regards to the unfulfilled PMR 2852-2:

1. If feasible, the Applicant could reopen the trial and enroll enough patients to reach 422 subjects (n=136).
2. If not feasible, then the Applicant will need to conduct another study and they should submit a meeting request to discuss their proposed new trial to fulfill the PMR.

11. Other Relevant Regulatory Issues

The clinical trials submitted with this application were under PREA PMRs, thus no additional exclusivity will be granted. Because the pivotal efficacy trial failed, we did not request OSI audits of the data.

12. Labeling

Prescribing Information
We recommend updating the USPI section 8.4 to describe the results of the completed pediatric trial.

Our proposed language (which is still under negotiation with the Applicant) is consistent with the FDA Guidance: Pediatric Information Incorporated Into Human Prescription Drug Labeling:

> The safety and effectiveness of SAVAYSA have not been established in pediatric patients with confirmed VTE (PE and/or DVT). Effectiveness was not demonstrated in an adequate and well-controlled study conducted in 145 SAVAYSA-treated pediatric patients, from birth to less than 18 years of age with confirmed VTE (PE and/or DVT), treated for 3 months up to a maximum of 12 months.

Other Labeling
Medication Guide
The medication Guide was revised as follows:

- Throughout the document the word "doctor" was changed to "healthcare provider" except where required by regulation (in the "What are the possible side effects of SAVAYSA?" section).
- A parenthetical reference to "(nonvalvular atrial fibrillation)" was added after the afib indication statement in the "What is SAVAYSA" section.
- Revised the pediatric use statement from "(b) (4)" to "It is not known if SAVAYSA is safe and effective in children with known deep vein thrombosis or pulmonary embolism."

13. Postmarketing Recommendations

There are no REMS associated with SAVAYSA.

The team recommends fulfilling PMR 2852-1 as the Applicant completed the requirements for that PMR.
The team recommends not fulfilling PMR 2852-2 as the Applicant did not complete the requirements for that PMR.

14. Recommended Comments to the Applicant

None.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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