JOINT CLINICAL, STATISTICAL and CLINICAL PHARMACOLOGY REVIEW

Application Type	sNDA
Application Number(s)	021345
Priority or Standard	Standard
Submit Date(s)	2/23/2024
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Division/Office	CDER/OND/OCHEN/DNH
Reviewer Name(s)	Kristen Snyder, MD and Donna Whyte-Stewart, MD, ScM
Review Completion Date	Electronic Stamp Date
Established/Proper Name	Fondaparinux Sodium
(Proposed) Trade Name	Arixtra
Applicant	Mylan Ireland Limited, a Viatris Company
Dosage Form(s)	Injection, solution
Applicant Proposed Dosing Regimen(s)	ARIXTRA 0.1 mg/kg subcutaneously once daily
Applicant Proposed Indication(s)/Population(s)	Treatment of venous thromboembolism (VTE) in pediatric patients aged 1 year or older
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of venous thromboembolism (VTE) in pediatric patients aged 1 year or older weighing at least 10 kg

Table of Contents

Table of Tables

Table of Figures

APPEARS THIS WAY ON ORIGINAL

Glossary

AC	advisory committee
ADaM	Analysis Data Model
AE	adverse event
aPTT	activated partial thromboplastin time
AR	adverse reaction
ASH	American Society of Hematology
ATIII	antithrombin III
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CHLA	Childrens Hospital of Los Angeles
CMC	chemistry, manufacturing, and controls
COA	Clinical outcome assessment
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRL	Complete Response Letter
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CVC	central venous catheter
CVST	cerebral venous sinus thrombosis
DMC	data monitoring committee
DOAC	direct oral anticoagulant
DVT	deep vein thrombosis
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice

GRMP	good review management practice
HIT	Heparin induced thrombocytopenia
HITT	heparin induced thrombocytopenia and thrombosis
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ISTH	International Society on Thrombosis and Hemostasis
ITT	intent to treat
IV	intravenous
LMWH	low-molecular weight heparin
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PE	pulmonary embolism
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SDTM	Study Data Tabulation Model
SGE	special government employee
sNDA	supplemental New Drug Application
SOC	standard of care
TEAE	treatment emergent adverse event
VKA	vitamin K antagonists

VTE venous thromboembolism

1. Executive Summary

1.1. Product Introduction

Fondaparinux (proprietary name Arixtra) is an anticoagulant that selectively binds to antithrombin III (ATIII) and neutralizes Factor Xa. Neutralization of Factor Xa interrupts the blood coagulation cascade and thus inhibits thrombin formation and thrombus development.

Arixtra was initially approved on December 7, 2001, for prophylaxis of deep vein thrombosis (DVT) which may lead to pulmonary embolism (PE) in adult patients undergoing hip fracture surgery, hip replacement surgery and knee replacement surgery.

On February 23, 2024, Mylan Ireland Limited submitted a supplemental New Drug Application (sNDA) for the treatment of venous thromboembolism (VTE) in pediatric patients aged 1 year or older. This supplement includes efficacy and safety data in pediatric patients with VTE from Study FDPX-IJS-7001 (Study 7001), a single-arm retrospective study. The proposed initial dosing regimen is fondaparinux 0.1 mg/kg subcutaneously (SC) daily, dose is optimized based on fondaparinux-based anti-Xa level.

The review team recommends approval for supplement-52. This prior approval supplement provides for a new indication for pediatric patients, for treatment of VTE in pediatric patients aged 1 year or older weighing at least 10 kg. This supplement also fulfills the following postmarketing requirements (PMRs); (1) PMR 2151-1 deferred pediatric study under PREA for the treatment of acute deep vein thrombosis when administered in conjunction with warfarin sodium in pediatric patients ages one to 16 years and (2) PMR 2151-2 deferred pediatric study under Pediatric Research Equity Act (PREA) for the treatment of acute PE when administered in conjunction with warfarin sodium in pediatric patients ages one to 16 years.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Study 7001 was a single arm, retrospective clinical study at a single tertiary center, Childrens Hospital of Los Angeles (CHLA) in which 366 pediatric patients aged 1 year and older were treated with fondaparinux, including Arixtra. In total, 325 patients with a diagnosis of VTE and who received at least one dose of fondaparinux were included in the efficacy analysis set. Of the 325 patients, 30 patients were <2 years, 65 patients were 2 to <6 years, 78 patients were 6 to <12 years, and 152 patients were 12 to <18 years. Patients were initiated on fondaparinux at 0.1 mg/kg once daily. Fondaparinux levels were monitored and dosing adjustments were made to achieve peak fondaparinux blood concentration within the therapeutic target of 0.5-1.0 mg/L.

Therapeutic fondaparinux levels were achieved in approximately 3 days. The primary endpoint was the proportion of patients with complete clot resolution defined as resolution of the clot with no residual thrombus seen at 3 months (± 15 days). Among 325 patients in the efficacy analysis set, 146 (44.9%; 95% CI: 39.6, 50.4) patients achieved complete clot resolution of at least one clot, and 143 (44%; 95% CI: 38.7, 49.4) patients achieved complete clot resolution of all clots. Results were consistent across age and weight subgroups.

Based on a review of a random-effects meta-analysis, the results of Study 7001 are consistent with efficacy results (same endpoints) reported in the literature for pediatric patients with VTE who receive standard of care anticoagulant/anti-thrombotic agents (low-molecular weight heparin (LMWH) and direct oral anticoagulants (DOAC)), thus demonstrating a similar physiological effect.

Substantial evidence of effectiveness was demonstrated based on results from Study 7001, an adequate and well controlled trial in pediatric patients with VTE and confirmatory evidence. Confirmatory evidence for this supplemental application is provided by existing adequate and well-controlled clinical studies in adult patients with VTE that demonstrated the effectiveness of fondaparinux for the approved indications (see Section 3.1 for a list of all approved indications). As the pathophysiology and clinical outcomes of VTE are similar to adults, it is reasonable to partially extrapolate efficacy data. Therefore, the prior determination of effectiveness of fondaparinux for the prevention and treatment of DVT and PE in adults is further evidence of effectiveness applicable to pediatric patients.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Pediatric VTE is a rare and serious disease associated with significant morbidity and mortality. VTE rates are rising, particularly in hospitalized children. Optimal management is critical to decrease VTE reoccurrence and related complications, while weighing the risk of bleeding. Standard of care treatment for VTE is anticoagulation. Multiple anticoagulants have been FDA-approved for the treatment of VTE in pediatric patients. Dalteparin, a LWMH product, is FDA-approved product for the treatment and secondary prevention of VTE in pediatric patients from birth and older. Dalteparin is administered twice daily, subcutaneously. Rivaroxaban, an oral factor Xa inhibitor, is indicated for the treatment of VTE and reduction in risk of recurrent VTE in pediatric patients from birth to less than 18 years of age. Dabigatran is an oral direct thrombin inhibitor indicated for the treatment and reduction in risk of reoccurrence in pediatric patients 3 months to less than 12 years of age. Other anticoagulants are commonly used off-label including heparin products and vitamin K antagonists (VKA).

The benefit-risk assessment for the treatment of VTE in pediatric patients was primarily based on Study 7001, a single-arm, retrospective study conducted at CHLA. The Applicant collected patient-level data including safety, efficacy and fondaparinux levels in pediatric patients who received at least one dose of fondaparinux (including Arixtra) at CHLA through December 31, 2018. The study included 366 pediatric patients between the age of 1 and <18 years, of which 325 patients were included in the efficacy analysis set. All age groups were well represented when considering the rarity of VTE in pediatric patients and allowed for an adequate analysis of efficacy and safety.

The efficacy of Arixtra was based on measuring the proportion of pediatric patients with complete clot resolution up to 3 months (±15 days). Although no formal hypothesis testing was included in the statistical analysis plan (SAP), a substantial number of patients achieved complete clot resolution. Among 325 patients in the efficacy analysis set, 44.9% (95% CI: 39.6, 50.4) achieved complete clot resolution of at least one clot, and 44% (95% CI: 38.7, 49.4) patients achieved complete clot resolution of all clots. Results were consistent across age and weight subgroups.

Similar to other anticoagulants, bleeding is a significant adverse reaction that can occur with fondaparinux, previously identified through adult studies. The incidence of major bleeding events, defined as per the International Society on Thrombosis and Hemostasis (ISTH) criteria, was the primary safety endpoint. Seven patients (1.9%) had composite major bleeding events and 11 patients (3%) had non-major bleeding events. No patient had a fatal bleeding event. Other adverse reactions that occurred during treatment with fondaparinux in pediatric studies included: anemia, thrombocytopenia, generalized skin associated events, abnormal liver function, hypokalemia, allergic reactions and hypotension.

The benefit-risk assessment supports regular approval of Arixtra for the treatment of venous thromboembolism (VTE) in pediatric patients aged 1 year or older and weighing at least 10 kg. Approval of Arixtra for pediatric patients fulfills an unmet need for additional anticoagulant options for pediatric patients. In addition, Arixtra has an advantage for once daily SC dosing.

Of note, there is no available prefilled syringe for patients weighing between 10-20 kg, and a patient specific dose should be prepared by the pharmacy and administered at home. Instructions for preparation of individual pediatric doses in pharmacies is described in the label.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• The incidence of VTE in the pediatric population has been estimated to be between 0.07 to 0.49 per 10,000 children per year [1]. • While overall VTE rates are lower in pediatric patients compared to adults, it is notable that VTE rates have been increasing in hospitalized children. • There are many risk factors that can contribute to the development of VTE including central venous catheters (CVCs), malignancy, infection, immobility, surgery, and thrombophilia, amongst others. • VTE may result in significant morbidity such as extremity pain and/or swelling, postthrombotic syndrome, organ dysfunction, pulmonary embolism, stroke, infection, prolonged hospitalization, loss of catheter function, and death.	VTE in pediatric patients is a rare and serious condition that is associated with significant morbidity and mortality.
Current Treatment Options	• Anticoagulation is the standard of care treatment for pediatric VTE, anticoagulation prevents acute and long-term complications. • Common anticoagulants used in pediatric patients include unfractionated heparin, LMWH, DOACs, and vitamin K antagonists. All anticoagulants have a risk of bleeding. • The following anticoagulants are FDA-approved:	There is an unmet need for additional FDA-approved anticoagulant options for pediatric patients.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	○ Dalteparin (LMWH) for the treatment of symptomatic VTE to reduce the recurrence in pediatric patients from birth and older. ○ Dabigatran (oral direct thrombin inhibitor) for the treatment and reduction of risk of recurrence of VTE in pediatric patients ages 3 months to less than 18 years. ○ Rivaroxaban (DOAC) for treatment of VTE and reduction in the risk of recurrent VTE in pediatric patients from birth to less than 18 years.	
Benefit	• Study 7001 was an open-label, single-arm retrospective study which evaluated the benefit-risk of Arixtra in 366 pediatric patients with VTE, at a single tertiary hospital. • In total, out of 366 patients, 325 patients with diagnosis of VTE were included in the efficacy analysis set, including 30 patients were <2 years, 65 patients were 2 to <6 years, 78 patients were 6 to <12 years, and 152 patients were 12 to <18 years. • In the efficacy analysis set, 44.9% (95% CI: 39.6, 50.4) of patients achieved complete clot resolution of at least one clot, and 44% (95% CI: 38.7, 49.4) patients achieved complete clot resolution of all clots. Results were consistent across age and weight subgroups. • Over 90% of patients reached the target therapeutic blood concentration with the initial dose and subsequent adjustments. • The median time to reach therapeutic levels across all age groups was approximately 3 days.	Study 7001 demonstrated that fondaparinux resulted in complete resolution of VTE in pediatric patients. The high percentage of patients reaching target levels, coupled with the consistency across age groups, supports the appropriateness of this dosing strategy.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• In total, 366 patients were included in the safety analysis set. • In Study 7001, 7 patients (1.9%) had composite major bleeding events: 1 patient (0.3%) had clinically overt bleeding (associated with a decrease in hemoglobin of at least 20 g/L (2 g/dL) in a 24-hour period), 3 patients (0.8%) had bleeding that was retroperitoneal, pulmonary, intracranial, or otherwise involved the central nervous system, and 3 patients (0.8%) had major bleeding that required surgical intervention in an operating suite. Eleven patients (3%) had non-major bleeding events and 65 patients (18%) had composite minor bleeding events. • Other adverse events included: anemia, thrombocytopenia, generalized skin associated events, abnormal liver function, hypokalemia, allergic reactions and hypotension.	The safety profile of fondaparinux is acceptable for pediatric patients with VTE. The safety profile is similar to observed toxicities in adult patients with VTE, including an increased risk for bleeding.

1.4. Patient Experience Data

No patient experience data was submitted as part of this supplemental application.

Patient Experience Data Relevant to this Application (check all that apply)

☐	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		[e.g., Sec 6.1 Study endpoints]
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Sec 2.1 Analysis of Condition]
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☒	Patient experience data was not submitted as part of this application.			

2. Therapeutic Context

2.1. Analysis of Condition

The precise number of people affected by DVT/PE is unknown, the Centers for Disease Control and Prevention (CDC) estimates as many as 900,000 people could be affected (1 to 2 per 1,000) each year in the United States with millions more internationally. The VTE incidence in pediatric population has been estimated between 0.07 to 0.49 per 10,000 children per year [1]. VTE rates have been increasing in hospitalized children, from 5.3 events per 10,000 pediatric hospital admissions in the early 1990s to 30-58 events per 10,000 hospital admissions in 2020 [2]. Many more adult patients than pediatric patients develop VTEs due to an increase number of acquired risk factors; thus, there are many more adult patients who could potentially participate in clinical trials for VTE prophylaxis and treatment.

There are differences in the etiology of VTE in pediatrics compared to the adults, in particular, in younger children. Genetic, anatomic, and acquired risk factors may impact the risk of developing VTE. Amongst pediatric patients, neonates and adolescents are at the highest risk for VTE [1]. The vast majority of VTEs occurring in children are provoked [3]. The most common provoking risk factor is the presence of central venous catheter (CVC) which attributes to >90% of VTEs in neonates and >60% in older children [1]. Other risk factors include cancer, sickle cell disease, congenital heart disease, trauma, thrombophilia, nephrotic syndrome, obesity, infection, inflammatory bowel disease, illness, medications, and inflammatory states [3]. Also, similar to adults, immobility, oral contraceptive use, and surgery are risk factors as well. Unprovoked VTEs do occur but are much less common. Often, pediatric patients have comorbidities, such as serious illness.

Similar to adults, VTE can lead to significant morbidity and mortality. VTE may result in postthrombotic syndrome, pain and/or swelling at the affected site, organ dysfunction, PE, stroke, infection, prolonged hospitalization, loss of catheter function and even death [2].

Treatment guidelines recommend anticoagulation for the initial treatment of symptomatic VTE in both adults and children. The goal of therapy is to prevent clot extension, embolism, and reoccurrence. The benefits of anticoagulation must be carefully weighed against the risk, most importantly the risk of bleeding [2]. Due to a lack of adequate and well controlled pediatric trials and overall paucity of data from pediatric studies, treatment recommendations are often based on the adult experience or observation. But, there are important considerations unique to pediatric patients this includes; developmental hemostasis, increased frequency of illness or comorbidities, vascular access issues, and heterogeneity within the pediatric population (i.e. age, weight, and risk factors) [2]. As VTE rates are increasing, with many patients with complex medical conditions, there is a significant unmet need for safe and effective anticoagulant for pediatric patients.

2.2. Analysis of Current Treatment Options

The most commonly used anticoagulants in children are unfractionated heparin (UFH), LMWH, fondaparinux, and VKA [1]. Currently, there are three FDA approved anticoagulants in children. First, dalteparin is a low molecular weight heparin (LMWH), given subcutaneously, approved in 2019 for the treatment of symptomatic VTE to reduce the recurrence in pediatric patients 1 month of age and older. In addition, the patient age was reduced to birth in 2024. The second was dabigatran, an oral direct thrombin inhibitor, approved in 2021 for the treatment and reduction of risk of recurrence of VTE in pediatric patients ages 3 months to less than 18 years. While UFH does not have a pediatric indication, pediatric dosing is described in the United States Prescribing Information (USPI). A summary of the commonly used anticoagulants in pediatrics is summarized in Table 1.

The American Society of Hematology (ASH) published guidelines in 2018 for the treatment of pediatric venous thromboembolism. In July 2022, these guidelines were reviewed by an expert work group convened by ASH and the committee agreed to continue monitoring evidence rather than revise or retire these guidelines. The guidelines recommend <3 months of treatment for provoked DVT or PE, and possibly longer if the causative risk factor persists. For unprovoked DVT or PE treatment was recommended for 6 to 12 months. Anticoagulation was also recommended for cerebral venous sinus thrombosis (CVST). The ASH guidelines suggest using LMWH or VKA for anticoagulation in patients with symptomatic DVT or PE. A recommendation on the use of DOACs were not made due to lack of available data from clinical trials [1]. For CVC-related VTE the 2012 American College of Chest Physicians Evidence-Based Clinical Practice Guidelines recommend that children should be treated with LMWH or UFH between 6 weeks and 3 months [4].

There is a clear unmet need for oral anticoagulants in pediatric patients. Unfractionated heparins and LMWHs require frequent monitoring and injections. VKAs are given orally, but also require frequent monitoring with venipuncture, in addition there is no approved liquid formulation, and INR levels are impacted by diet and concomitant medications. DOACs were just recently approved for pediatric patients and are used less commonly in younger patients. In addition, long-term safety data is lacking.

Table 1. Summary of Treatment Armamentarium Relevant to Proposed Indication

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments (e.g., subpopulation not addressed
FDA Approved Treatments						
Dabigatran capsules and oral pellets	1) For the treatment of venous thromboembolic	2021	Oral twice daily, weight based	Based on extrapolation from adult trials and	In pediatric trials the major safety issue was bleeding	Approval does not cover the entire pediatric age

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments (e.g., subpopulation not addressed
(DOAC)	events (VTE) in pediatric patients aged 3 months to less than 18 years of age who have been treated with a parenteral anticoagulant for at least 5 days 2) To reduce the risk of recurrence of VTE in pediatric patients aged 3 months to less than 18 years of age who have been previously treated			pediatric clinical trials	Gastrointestinal adverse reactions Alopecia	range
Dalteparin injection (LMWH)	Treatment of symptomatic venous thromboembolism (VTE) to reduce the recurrence in pediatric patients from birth (gestational age at least 35 weeks) and older	2019	Subcutaneous Injection twice daily, based on age	Based on extrapolation from adult trials and pediatric clinical trials	In pediatric trials the major safety issue was bleeding Heparin induced thrombocytopenia (HIT) or heparin induced thrombocytopenia and thrombosis (HITT) Hypersensitivity	
Rivaroxaban (DOAC)	Treatment of VTE and reduction in the risk of recurrent VTE in pediatric patients from birth to less than	2021	Oral based on body weight	Open-label, active-controlled, randomized study	In pediatric trials the major safety issue was bleeding	

Product (s) Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments (e.g., subpopulation not addressed
	18 years. For thrombo-prophylaxis in pediatric patients 2 years and older with congenital heart disease after the Fontan procedure.					
Other Treatments – Not FDA approved for pediatric patients						
Heparin (UFH)			Intravenous Initial Dose 75 to 100 units/kg IV bolus over 10 minutes Maintenance dose: Infants: 25-30 units/kg/hour Children: >1 year of age: 18 to 20 units/kg/hour	Target aPTT of 60-85 secs assuming this reflects an anti-Xa level of 0.35 to 0.70	Bleeding risk HIT and HITT Hypersensitivity Antidote-protamine	Dosing for pediatric patients is described in the USPI Use preservative-free heparin sodium injection in neonates and infants

Source: Clinical Reviewer
Abbreviations: DOAC = direct oral anticoagulant; VTE = venous thromboembolism, HIT= Heparin induced thrombocytopenia; HITT= heparin induced thrombocytopenia and thrombosis; UFH=unfractionated heparin; aPTT= activated partial thromboplastin time; IV=intravenous; USPI= United States Package Insert

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Fondaparinux (Arixtra) was approved December 7, 2001. The approved indications for fondaparinux are:

- For the prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE):
    - in patients undergoing hip fracture surgery, including extended prophylaxis;

  - in patients undergoing hip replacement surgery;
  - in patients undergoing knee replacement surgery;
  - in patients undergoing abdominal surgery who are at risk for thromboembolic complications.
- For the treatment of acute deep vein thrombosis when administered in conjunction with warfarin sodium.
- For the treatment of acute pulmonary embolism when administered in conjunction with warfarin sodium when initial therapy is administered in the hospital.

Postmarketing requirements for the study of Arixtra in pediatric patients with VTE were issued in the May 28, 2004 approval letter for S-004 and S-005:

> PMR 2151-1: Deferred pediatric study under PREA for the treatment of acute deep vein thrombosis (DVT) when administered in conjunction with warfarin sodium in pediatric patients ages birth to 16 years.
>
> PMR 2151-2: Deferred pediatric study under PREA for the treatment of acute pulmonary embolism (PE) when administered in conjunction with warfarin sodium in pediatric patients ages birth to 16 years.

(b) (4)

(b) (4)

On May 2, 2014 the Agency waived the pediatric study requirement for ages birth to less than one year of age because necessary studies were impossible or highly impracticable and released the Sponsor of the above PMRs on May 2, 2014. The following PMRs were reissued:

1. PMR 2151-1: Deferred pediatric study under PREA for the treatment of acute deep vein thrombosis when administered in conjunction with warfarin sodium in pediatric patients ages one to 16 years.
2. PMR 1194-2: Deferred pediatric study under PREA for the treatment of acute pulmonary embolism when administered in conjunction with warfarin sodium in pediatric patients ages one to 16 years.

3.2. Summary of Presubmission/Submission Regulatory Activity

Table 2 summarizes the relevant regulatory history pertaining to this sNDA.

Table 2. Regulatory History

Date	Regulatory History
September 8, 2011	A Type C meeting occurred to discuss and agree on next steps to support labeling for pediatric patients and to fulfill PREA PMRs. The Agency recommended the Applicant conduct "a well-designed PK/PD and clinical outcomes study" in pediatric patients.

(b) (4)

Date	Regulatory History
	(b) (4)
May 14, 2014	NDA 021345 transferred from GalaxoSmithKline to Aspen Global, Incorporated.
	(b) (4)
October 24, 2014	Aspen Global, Inc transferred ownership of NDA 021345 to Mylan Ireland Limited (b) (4) .
June 13, 2016	(b) (4)
January 26, 2018	(b) (4) (b) (4) In addition, comments included: • The FDA requested randomized trial(s) to study the safety and efficacy of fondaparinux in children 1 to 18 years of age. • The FDA stated that if the Applicant demonstrates that reasonable attempts to develop a commercially marketable formulation have failed, they must develop and test an age-appropriate formulation that can be prepared by a licensed pharmacist, in a licensed pharmacy, from commercially available ingredients.

Date	Regulatory History
April 27, 2020	Mylan was issued a PREA Non-compliance letter for failure to submit either a pediatric assessment or request deferral extension to meet the PMR of the PREA for this application.
June 16, 2020	The Applicant submitted a request for a deferral extension and proposed revised milestones for PMRs 2151-1 and 2151-2.
December 17, 2020	The Agency issued a Deferral Extension Granted letter regarding the final report submission date and revised milestone due dates for PMRs 2151-1 and 2151-2 allowing a deferral extension date from 12/2019 to 06/2021 due to delays involving patients, sites, and/or management.
March 30, 2021	The Applicant submitted a request for a deferral extension and proposed revised milestones for PMRs 2151-1 and 2151-2.
May 14, 2021	The Agency issued a Deferral Extension Granted letter regarding the final report submission date and revised milestone due dates for PMRs 2151-1 and 2151-2 allowing a deferral extension date from 06/2021 to 12/2022 due to delays due to issues with the study drug and/or comparator drug and additional time required to prepare the study report and/or submission.
October 4, 2021	The Applicant submitted a proposal for a retrospective study (7001). The Agency advised the Applicant: ▪ All pediatric patients who received at least one dose of fondaparinux should be included. ▪ The study must include a literature based historical control to understand efficacy. ▪ The application needs a comprehensive human factors study plan.
November 16, 2021	The Agency Advice/Information Request specified: ▪ (b) (4)

Date	Regulatory History
	(b) (4) ▪ The primary analysis population should be based on all available patients exposed to fondaparinux to avoid biased results. ▪ Because a concurrent control arm is not possible, the Applicant should provide a literature-based pediatric historical control assessment for all primary and secondary endpoints. ▪ Provide a case-based explanation for patients initially identified as receiving at least one dose of fondaparinux but were determined not to receive fondaparinux. ▪ Treat those patients who had missing data or are dropouts after the study start date as non-responders (or failures) in the primary analysis. ▪ Collect the following: 1) use of other forms of VTE treatment, such as thrombolytic therapy and interventional radiology treatments. 2) Identify if VTE events were symptomatic or asymptomatic; context of incidental findings, reasons for treatment of asymptomatic VTE events 3) Specific timing of fondaparinux anti-Xa evaluation and number of stable doses after which the testing was done.
November 22, 2021	The Applicant responded with amended definitions: (b) (4)
November 26, 2021	(b) (4)

Date	Regulatory History
	(b) (4) • Furthermore, for comprehensive safety evaluation of the proposed approach, it is crucial to have access to all exposed patients, not most of the exposed patients, as indicated in [the Sponsor's] response.
December 13, 2021	The Applicant acknowledged the Agency's feedback stating there were four patients who received fondaparinux at CHLA **prior** to January 1, 2008 and they would be included in the proposed safety dataset.
January 26, 2023	(b) (4)
February 28, 2023	The Agency issued a Notification of Non-compliance with PREA Letter for failing to meet the PMR of the PREA after not submitting pediatric assessments for PMRs 2151-1 and 2151-2 which were deferred until December 30, 2022.
September 29, 2023	The retrospective study (7001) Clinical Study Report was submitted to the Agency to fulfill PREA PMR study numbers 2151-1 and 2151-2.
February 23, 2024	The sNDA was filed under 505(b) of the Federal Food, Drug, and Cosmetic Act for NDA 021345 supplement number 052.

3.3. Foreign Regulatory Actions and Marketing History

Arixtra is marketed in the United States and Europe. No country has an indication for pediatric patients. See Table 3 below.

Table 3. Arixtra Approvals and Marketing Countries

Countries with MA Approval	Marketed (Yes/No)	Pediatric Indication (Yes/No)
Albania	No	No
Bosnia and Herzegovina	Yes	No
European Union, Iceland, Norway, Lichtenstein	Yes	No

Countries with MA Approval	Marketed (Yes/No)	Pediatric Indication (Yes/No)
Macedonia	Yes	No
Moldova	No	No
Montenegro	Yes	No
Serbia	Yes	No
Switzerland	Yes	No
United Kingdom	Yes	No
United States	Yes	No

Abbreviations: MA= marketing approval
Source: Applicant's Information Response dated November 22, 2024

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Not applicable. An OSI audit was not requested as a single retrospective chart review study was submitted for review.

4.2. Product Quality

The Product Quality review team recommends to approve this efficacy supplement. See finalized review.

The reviewer states pediatric preparations of Arixtra will be performed in pharmacies by transferring commercial Arixtra® into a sterile empty vial, then into new syringes, and stored at 2-8˚C for up to 30 days prior to use by "pharmacy compounding practice" (repackaging process). The updated PI changes are related to dosing of pediatric patient aged 1 year and older weighing 10-20 kg as well as instructions for preparation of individual pediatric doses in pharmacies. The proposed dosing for the pediatric population is 0.1 mg/kg. This is lower than the highest approved dose (0.15 mg/kg) for the adult population.

Mylan generated stability data that supports compatibility with a 1 mL tuberculin syringe (representative of commercial suppliers) for 14 days and 30 days at both 2–8°C and at room temperature, a microbiological evaluation supporting the proposed pharmacy compounding instructions, and a microbial challenge study that simulated gross failure during a pharmacy

preparation procedure using both strengths of Arixtra (5 mg/mL and 12.5 mg/mL), and chemical compatibility studies of Arixtra in prefilled glass vials and insulin syringes. Mylan had also proposed use of insulin syringes, however, the product quality team concluded the insulin syringe is not appropriate for non-insulin products due to risk of medication errors (i.e., insulin syringes are marked in units and this product is measured in mL).

Mylan's studies have demonstrated it is possible to extract the desired dose for a pediatric patient. Additionally, the Applicant, Mylan, confirms the Beyond Use Date (BUD) of the prepared sterile preparation of Arixtra is 30 days from the date of preparation when stored refrigerated at 2-8°C or at ambient conditions (15-25°C).

4.3. Clinical Microbiology

The Clinical Microbiology team has determined that the proposed changes to labeling based on data submitted in this efficacy supplement are adequate. See finalized review dated November 14, 2024.

The reviewer notes that the justification for not manufacturing the pediatric formulation by aseptically filling into syringes and release testing for bacterial endotoxins and sterility appears reasonable based on the IR response and the previous IND 51126 consult micro review memo (IND 51126 consult 20220214). The prepared pediatric preparations are intended for use in patients treated at the hospitals, outpatient clinics, and at home. While the reviewer notes that the pediatric preparation procedure by repackaging of commercial product for extended storage is discouraged, preparations of pediatric doses immediately prior to administration or non-extended storage are not feasible for non-hospital uses.

The microbiology team provided comments related to reducing potential microbial contamination during the pediatric dosing preparation and storage and this was incorporated appropriately into labeling. Comments include adding details of aseptic technique, updating syringe and needle as "sterile" syringe and "sterile" needle, specifying the empty vial as "closed/sealed", clarifying the policy on pooling commercial Arixtra into a vial, adding packing process following the completion of pediatric dosing preparations, and adding a statement for avoiding post-repackaging storage at room temperature.

Of note, the Applicant uses the term "Pharmacy Compounding" for the proposed pediatric dosing preparation by transferring the commercial product into a new syringe through an empty vial. OND requested a consult to the Office of Compounding for input and recommendations for review of this application. The review team had an internal discussion with the Office of Compounding team on 7/16/2024. The Office of Compounding states that the proposed pediatric dosing preparation is NOT considered as Pharmacy Compounding based on the definition of Pharmacy Compounding, instead, it is considered as repackaging.

4.4. Nonclinical Pharmacology/Toxicology

Not applicable. No new non-clinical data was submitted with this application.

4.5. Clinical Pharmacology

The clinical pharmacology review team reviewed the appropriateness of the proposed dosing algorithm of fondaparinux in pediatric patients. Refer to section 7.1.4 for the assessment. No significant issues were identified.

4.6. Devices and Companion Diagnostic Issues

None.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Table 4. Listing of Clinical Trial Relevant to this sNDA

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
	Controlled Studies to Support Efficacy and Safety						
FDPX-IJS-7001	Retrospective cohort study to evaluate long-term dosing, efficacy, and safety of fondaparinux for treatment of venous thromboembolism in pediatric patients.	0.1 mg/kg once daily, subcutaneously.	Primary: Proportion of patients with complete clot resolution at 3 months Secondary: • Proportion of patients with complete or partial clot resolution • Proportion of patients with VTE recurrence at 1 year • Proportion of patients with VTE recurrence anytime during the treatment.	Varied based on clot resolution	366 patients	pediatric patients aged <18 years	1 Center 1 Country: US

5.2. Review Strategy

The review is a joint review by the clinical, statistical, and clinical pharmacology teams. The primary clinical reviewers were Kristen Snyder and Donna Whyte-Stewart, and their team leader was Carrie Diamond. The primary statistical reviewer was Fei Wu, and his team leader was Yeh-Fong Chen. The primary clinical pharmacology reviewer was Yaning Sun and his team leader was Sudharshan Hariharan.

This review will also serve as the Cross-Discipline Team Leader (CDTL) review.

The review of efficacy and safety was based on the analysis of Study 7001.

The Applicant submitted this efficacy sNDA to the FDA Center for Drug Evaluation and Research (CDER) Electronic Document Room. The data included in this submission are in electronic Common Technical Documents Format, in accordance with FDA guidance on electronic submission. The datasets included definition files.

The key materials used for the review of efficacy and safety include the following:
- sNDA 021345/S052 including: clinical study reports (CSR), patient narratives, the protocol and amendment, statistical analysis plan and amendments, and data sets.
- Relevant published literature.
- Relevant information in the public domain.

Clinical data were provided in the Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM). The clinical and statistical reviewers were able to duplicate the analysis based on the Applicant's submitted datasets.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study FDPX-IJS-7001 (7001)

6.1.1. Study Design

Overview and Objective

Trial name: Retrospective Cohort Study to Evaluate Long Term Dosing, Efficacy, and Safety of Fondaparinux for Treatment of Venous Thromboembolism in Pediatric Patients.

Study 7001 was a retrospective, single center, open-label study in patients treated with at least one dose of fondaparinux at CHLA. The primary objective of this study was to determine the

proportion of pediatric patients that achieve fondaparinux blood concentrations within a therapeutic range based on peak blood concentrations and describe measures of safety and effectiveness.

Trial Design

Study 7001 was an uncontrolled, non-randomized, retrospective study conducted in pediatric patients less than 18 years of age treated with at least one dose of fondaparinux at a single center, CHLA through December 31, 2018. Pediatric patients were identified from electronic pharmacy records for screening and included in the study based on eligibility criteria. Retrospective data of patients receiving fondaparinux (Arixtra or generic fondaparinux) were collected and evaluated for safety, efficacy, and PK analysis. CHLA followed a defined institutional clinical practice overseen by hematologists. Identified patients were treated either on the prospective FondaKIDS study, a pilot dose finding and PK study of fondaparinux in children with thrombosis [7] or not on a study but by use of an institutional clinical practice protocol. The fondaparinux clinical practice protocol included guidance on initial fondaparinux dosing, timing of anti-Xa levels, dose adjustments, and timing of follow-up imaging studies.

Clinical reviewer comment: *The Applicant has conducted a retrospective study to assess PK, efficacy, and safety in the pediatric population. At the time PMRs were issued, the only anticoagulant product available for comparison in the pediatric population was enoxaparin sodium injection, a twice daily injection that is not FDA approved for pediatric use. A study comparing these two products in blinded-fashion would have required patients randomized to fondaparinux or a second sham injection daily which likely would have made recruitment impractical. In addition, given the rarity of VTE in the pediatric population, and now changing therapeutic landscape for anticoagulants (i.e., more anticoagulants available and increased use of oral anticoagulants), this study design is reasonable.*

Of note, patients were administered Arixtra® (commercial brand Arixtra) until July 10, 2011. Starting July 11, 2011, CHLA switched to commercially available generic fondaparinux.

Trial location
All patients included in Study 7001 were treated at CHLA in Los Angeles, California.

Clinical reviewer comment: *While the study was conducted at a single center, results are considered generalizable to the US population given CHLA is a large tertiary hospital and referral center for pediatric patients with VTE. In addition, pediatric VTE is typically managed by physicians who specialize in the care of VTE.*

Choice of control group
The study had no concurrent control group.

Clinical reviewer comment: *The Applicant included historical studies and literature review for comparison of efficacy claims.*

Key inclusion/exclusion criteria

Inclusion Criteria: Eligible patients included male and female pediatric patients aged < 18 years at the time of initiation of treatment with fondaparinux.

Exclusion Criteria: Patients were ineligible if they had insufficient medical records to extract the required data (age, diagnosis, use of fondaparinux, duration of treatment).

Dose selection and adjustment

See justification for proposed dosing in Section 7.2 of this review.

In Study 7001, patients weighing more than 20 kg received initial fondaparinux dosing of 0.1 mg/kg once daily SC with doses rounded to the nearest prefilled syringe (2.5 mg, 5 mg, or 7.5 mg). Patients weighing 10 kg to 20 kg were treated with an initial dose of 0.1 mg/kg once daily SC with doses rounded to the nearest 0.1 mg (Table 5) with a maximum initial dose not to exceed 7.5 mg/day. Fondaparinux doses were prepared in the CHLA pharmacy.

Table 5. Dosing of Fondaparinux for Treatment of Deep Vein Thrombosis*

Body Weight (kg)	Dose (mg/kg)	Actual Total Dose/Comments
10-20	0.1	Dosing should be exact and rounded to the nearest 0.1 mg
20-40	0.1	Initial dose should be 2.5 mg prefilled syringe
40-60	0.1	Initial dose should be 5 mg prefilled syringe
>60	0.1	Initial dose should be 7.5 mg prefilled syringe

*For dose adjustments, Table 5 was used to estimate the dose adjustment based on anti-Xa levels.
Source: Applicant's CSR

Clinical reviewer comment: *The doses actually administered were determined using baseline body weights of patients based on the following categories: 10-20 kg, >20-40 kg, >40-60 kg, and >60 kg. This will be reflected in labeling.*

As safety and efficacy was not evaluated in patients weighing less than 10kg, the Agency recommended to indicate fondaparinux only for patients 10kg or above.

The therapeutic target of 0.5 to 1 mg/L was established from prior adult and pediatric (FondaKIDS) experience. Dose adjustments (Table 6) were made based on fondaparinux levels measured using a chromogenic anti-Xa assay with a fondaparinux-specific calibration curve. Levels were obtained 3 hours after every second or third dose until therapeutic levels were achieved. Fondaparinux levels were monitored weekly while patients were admitted and approximately every 1-3 months outpatient while patients remained on treatment.

Table 6. Dose Adjustment of Fondaparinux for Treatment of Deep Vein Thrombosis*

Fondaparinux-based Anti-Xa Levels (mg/L)	Dose Adjustment
<0.3	Increase dose by 0.03 mg/kg
0.3-0.5	Increase dose by 0.01 mg/kg
0.5-1	No change
1-1.2	Decrease dose by 0.01 mg/kg
>1.2	Decrease dose by 0.03 mg/kg

*Doses rounded to the nearest 0.1 mg.
Source: Applicant's CSR

Clinical reviewer comment: *The dose of fondaparinux was identified based on the FondaKIDS study, a pilot, dose-finding and PK study in 24 pediatric patients aged 1-18 with DVT or heparin-induced thrombosis (HIT) [5]. Patients were dosed at 0.1 mg/kg/day in the FondaKIDS trial in which patient weights ranged from 8 kg to 130 kg. It is not clear from the reference how doses were rounded, if pre-filled syringes were used, or the maximum dose allowed. Peak fondaparinux levels were obtained 2, 4, 12 and 24 hours after the first dose and measured using a fondaparinux-based chromogenic anti- Xa assay. Subsequent levels were obtained at 4 hours after dose administration. Levels from 0.5 to 1 mg/L were considered therapeutic in the FondaKIDS study.*

In contrast to the FondaKIDS study, in Study 7001, levels were obtained at both a different time post dose as well as a different dose; i.e. peak levels of fondaparinux were obtained 3 hours post second dose (as opposed to 4 hours following first dose). In both studies, pediatric fondaparinux levels were considered therapeutic if they were 0.5 to 1 mg/L.

Assignment to treatment
All patients in Study 7001 were treated with Arixtra® or fondaparinux. There was no randomization nor stratification.

Blinding
There was no blinding in FDX-IJS-7001.

Dose modification, dose discontinuation
Doses, dose adjustments, and treatment duration were collected from electronic medical records and CHLA's pharmacy database. Based on Clinical Study Protocol 7001, dose adjustments were based on levels achieved at approximately 2.5 to 3.5 hours after every second dose. Dose adjustments are described in Table 6 above.

Doses were held for invasive procedures. For minor procedures such as lumbar punctures, bone marrow aspirations, chest tube placement, central venous catheter placement, etc., fondaparinux was held for 24 hours (the dose on the day of the procedure is omitted assuming

the patient is being dosed in the morning). For major surgical procedures, fondaparinux was held for 48 hours (the dose the day before and the day of the procedure are omitted).

Administrative structure

There was no administrative structure, data monitoring committee, adjudication committee involved in the study conduct. Only investigators at CHLA assessed effectiveness and safety of fondaparinux treatment.

Procedures and schedule

There was no protocol planned schedule of procedures or events. The Applicant reported that patients treated with fondaparinux at CHLA followed a defined institutional clinical practice such that each patient's treatment plan including anticoagulant choice, initial dosing and dose adjustments of fondaparinux, timing of fondaparinux levels, and follow-up imaging studies were "largely the same".

Data for vital signs, physical examination, other safety observations, and clinical laboratory data for safety parameters (hematology, chemistry, urinalysis) were not collected as part of this retrospective protocol.

Concurrent medications

Per the protocol for Study 7001, information on concomitant medication with respect to indication, daily dose, and start and stop dates was to be documented. However, the Applicant reported protocol deviations for data collection with respect to concomitant medications stating that "due the retrospective nature of the study and patient population with significant comorbidities, site staff was finding it difficult to capture detailed information on concomitant medications in a reasonable time frame." The Applicant captured concomitant medication names and other readily available information in the source documents.

Clinical reviewer comment: *A limitation of the study is concomitant medications were not fully documented due to feasibility of capturing concomitant medication data, leading to a significant number of protocol deviations. Allowing the site to capture only concomitant names and other "readily available information" is an error of omission and may impact efficacy and safety assessments.*

Treatment compliance

During hospitalization, fondaparinux was administered by hospital staff and captured as part of the medical chart. However, after discharge to home, compliance was captured based on blood levels obtained every 1 to 3 months. Medication calendars or diaries were not required.

Patient completion, discontinuation, or withdrawal

Due to the retrospective nature of Study 7001, patients were not considered as "completing" or withdrawing from the study and no patients were replaced. Those who discontinued

fondaparinux due to AE, change to a different anticoagulant, and other reasons were identified in the medical record and on the CRF. Patients who died up to data cut off either while receiving fondaparinux or following discontinuation of fondaparinux for any reason were included in narrative summaries. All patients were included in the efficacy analysis if they received one dose of fondaparinux and had a VTE documented.

Study Endpoints

Primary Endpoints

The primary efficacy endpoint is the proportion of patients achieving complete clot resolution during the period of up to 3 months, where complete clot resolution is defined as no residual thrombus seen by evaluation.

The primary PK endpoint is the proportion of patients with peak blood concentration measurements of fondaparinux within a therapeutic target of 0.5 to 1.0 mg/L.

The primary safety endpoint is the incidence of major bleeding, a composite of the following:

- Fatal bleeding
- Clinically overt bleeding associated with a decrease in hemoglobin (Hb) of at least 20 g/L (2 g/dL) in a 24-hour period.
- Bleeding that was retroperitoneal, pulmonary, intracranial, or otherwise involved the central nervous system (CNS); and
- Bleeding that required surgical intervention in an operating suite.

Secondary Endpoints

The secondary efficacy endpoints include the following:

- Proportion of patients with complete or partial clot resolution.
- Proportion of patients with VTE recurrence at one year.
- Proportion of patients with VTE recurrence anytime during the treatment.

Secondary PK endpoints include the following:

- Post-dose peak blood concentration of fondaparinux (in mg/L).
- Proportion of patients with peak blood concentration measurements of fondaparinux in three categories: within therapeutic target, supratherapeutic, and subtherapeutic.
- Frequency of fondaparinux dosing adjustments (number of adjustments, number of days between adjustments).
- Time (in days) from the first dose until the therapeutic dose (defined as the dose that results in fondaparinux blood concentrations in the target range) was achieved.

The secondary safety endpoints include the following:

- Clinically relevant non-major bleeding, a composite of the following:
    - Overt bleeding for which a blood product was administered, and which was not directly attributable to the patient's underlying medical condition.
    - Bleeding that required medical or surgical intervention to restore hemostasis, other than in an operating room.
- Minor bleeding events, defined as follows:
    - Any overt or macroscopic evidence of bleeding that did not fulfill the above criteria for either major bleeding or clinically relevant, non-major bleeding.
    - Menstrual bleeding resulting in a medical consultation and/or intervention.
- Overall mortality.
- VTE-related mortality.
- Proportion of patients with post-thrombotic syndrome (PTS)
- Other AEs of interest (selected as they have been observed for fondaparinux in clinical trials or potentially serious events seen in post-marketing and were amenable to abstraction from the patient medical record):
    - Anemia
    - Events of thrombocytopenia
    - Allergic reactions
    - Events of hypokalemia
    - Events have decreased blood pressure and hypotension
    - Abnormal liver function tests
    - Local and generalized skin-associated events

Clinical reviewer comment: *The efficacy, safety, and pharmacokinetic analysis groups and endpoints were discussed with the Agency during the IND stage and agreed upon. Due to the retrospective nature of the study, some patients may have had thrombosis resolution and stopped anticoagulant therapy prior to the 3-month evaluation. Therefore, the primary efficacy endpoint used was the proportion of patients achieving complete clot resolution during the period of up to 3 months. In clinical practice, patients with clot resolution may stop anticoagulation at the time of thrombus resolution, even if prior to a 3-month evaluation, therefore this primary efficacy endpoint is reasonable.*

Major, clinically relevant non-major and minor bleeding definitions were consistent with standardized definitions according to ISTH guidelines [6].

Statistical Analysis Plan

The Applicant's SAP was dated September 21, 2022. This is a retrospective cohort study, and the data were collected before the SAP was finalized. The Agency did not review the SAP.

The study is descriptive. There was no formal hypothesis testing planned. For binary endpoints (such as 'complete resolution', 'complete resolution or partial resolution' of clot), Wilson Score

method was used to calculate the confidence intervals for the proportions. Time to event endpoints, such as time to first 'Complete clot resolution', was analyzed by the Kaplan Meier method.

The study populations were defined as follows:

- Safety Analysis Set: The safety analysis set included all patients who received at least 1 dose of fondaparinux through December 31, 2018. Patients with insufficient medical records were excluded from the Safety Analysis Set.
- Efficacy Analysis Set: Efficacy analysis set included all patients from Safety analysis set with the diagnosis of VTE.
    - Efficacy Subgroup: The efficacy subgroup included the patients from efficacy analysis set meeting the following criteria:
        - Treated with fondaparinux for at least 14 days.
        - Availability of follow-up imaging at 3 months (± 15 days).
        - Anticoagulant treatment other than fondaparinux (most commonly heparin or enoxaparin) for not more than 33% of the treatment duration up to the discontinuation of fondaparinux.

      The efficacy subgroup was used for sensitivity analyses.

Patients with missing data were considered as 'non-responder' for the analysis of the primary efficacy endpoint.

There was no planned interim analysis for this study.

The study included subgroup analyses based on weight (<20kg, 20-40kg, 40-60kg, >60kg) and age (< 2 years, ≥ 2 to < 6 years, ≥ 6 to <12 years, ≥ 12 to < 18 years).

Protocol Amendments

There was one protocol amendment, Version 2.0 dated July 22, 2022. The protocol was amended based on the initial Institutional Review Board (IRB) review.

In section 1.4 and 9.8 of the protocol, the existing text "patient-level data will be collected in an anonymized fashion without any patient identifiers" was replaced with the following: "Each patient enrolled in the study will be assigned a coded study number. CHLA will maintain their own restricted electronic file that links the CRF with the patient's name and medical record number. This information will not be shared with Mylan. The data elements to be collected are described in section 6 of the protocol". There were no other amendments to the protocol.

Clinical reviewer comment: *This amendment was minor and had no impact on the integrity of the trial or interpretation of results.*

6.1.2. Study Results

Compliance with Good Clinical Practices

Study 7001 was conducted in accordance with the protocol, applicable regulations, the ethical principles set forth in the Declaration of Helsinki, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Harmonized Guideline for Good Clinical Practice (GCP) E6 (R2). The IRB reviewed and approved the study per 45 CFR 46.110/21 CFR 56.110, Federal Register expedited category 5, determined children may be included in the research, and the research meets the requirements of 45 CFR 46.404/21 CFR 50.51. The research involved no greater than minimal risk to patients.

Financial Disclosure

A signed form 3454 was submitted to the Agency upon request. There were no financial interests or arrangements with clinical investigators.

Patient Disposition

Table 7 represents a summary of patient disposition for Study 7001. Of 379 patients screened, 13 patients were considered screen failures while 366 (100%) patients were treated with at least one dose of fondaparinux at CHLA and included in the safety analysis set (SAF). Of 366 patients, 325 (88.8%) were considered evaluable for efficacy and 209 (57.1%) patients completed treatment. Nineteen (5.2%) patients remained on fondaparinux at the end of study (December 31, 2018).

Table 7. Study 7001 Patient Disposition

	Fondaparinux N= 366 n (%)
Screened	379
Screen failures	13
Exposed/included in safety analysis set	366 (100)
Efficacy analysis set	325 (88.8)
Efficacy subgroup	221 (60.5)
Completed treatment	209 (57.1)
Ongoing treatment with fondaparinux at end of study	19 (5.2)
Withdrawn from study treatment	132 (36.1)
Adverse Event	22 (6)
Change anticoagulant	63 (17.2)
Withdrawal by participant	10 (2.7)

	Fondaparinux N= 366 n (%)
Lost to follow-up or unknown	22 (6)
Other	6 (1.6)
Death*	12 (3.3)

*Deaths occurring on-treatment and up to 30 days after last dose of fondaparinux.
Source: FDA reviewer analysis

Clinical reviewer comment: *The Agency issued an information request (IR) (July 18, 2024) to clarify the number of patients analyzed for efficacy after patients with VTE. The Agency was concerned that not all eligible patients were included in the efficacy analysis set, some were noted to not have an efficacy flag in the dataset. The Applicant identified 12 patients (already included in the safety analysis set) for whom efficacy flags were omitted in error (Patients* (b) (6) *) increasing the number of patients who should have been included in the Efficacy Analysis Set to 325 (not 313, as originally proposed by the Applicant).*

Protocol Violations/Deviations

The Applicant was unable to collect all protocol required data for concomitant medications and protocol deviations occurred. As per the protocol, information on concomitant medication with respect to indication, daily dose, and start and stop dates was expected to be documented. However, due to the retrospective nature of the study and patient population with significant comorbidities, site staff found it difficult to capture detailed information on concomitant medications in a reasonable time frame. Therefore, only concomitant medications names and other readily available information were captured in the source documents.

Clinical reviewer comment: *The deviations in data collection for concomitant medications could have influenced the safety and efficacy results of the study. For example, if a concomitant medication causing hypotension was administered and the patient developed hypotension, it may be difficult to identify if the hypotension was related to fondaparinux or the concomitant medication. However, the safety data in pediatrics based on this study is similar to that of adults suggesting the deviation in concomitant medication was unlikely to influence study results.*

Table of Demographic Characteristics

Table 8 Demographic Characteristics of the Primary Efficacy Analysis Set

Demographic Parameters	**Efficacy Analysis Set (N= 325)**
Sex, n (%)	
Male	158 (48.6)

Demographic Parameters	Efficacy Analysis Set (N= 325)
Female	167 (51.4)
Age (years)	
Mean years (SD)	9.57 (5.46)
Median (years)	11
Min, max (years)	0.5, 17.0
Age Group, n (%)	
< 2 years	30 (9.2)
≥ 2 to < 6 years	65 (20.0)
≥ 2 to < 12 years	78 (24.0)
≥ 12 to < 18 years	152 (46.8)
Race, n (%)	
White	76 (23.4)
Black or African American	26 (8.0)
Asian	20 (6.2)
American Indian or Alaska Native	-
Native Hawaiian or Other Pacific Islander	1 (0.3)
Other	154 (47.4)
Unknown/Missing	48 (14.8)
Ethnicity	
Hispanic or Latino	118 (36.3)
Not Hispanic or Latino	120 (36.9)
Unknown/Missing	87 (26.8)
Body Weight at Baseline (kg)	
Median	34.9
Mean (SD)	40.54 (26.55)
Min, Max	3.27, 139.9
Missing	1
Body Weight Category at Baseline, n (%)	
<20 kg	95 (29.2)
20-<40 kg	84 (25.8)
40-<60 kg	72 (22.2)
>=60 kg	73 (22.5)
Missing	1 (0.3)

Source: FDA reviewer's analysis

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

Table 9: Other Baseline Characteristics of the Primary Efficacy Analysis Set

Demographic Parameters	Efficacy Analysis Set (N= 325) n (%)
Number of VTEs	
< 2	276 (84.9)
>= 2	38 (11.7)
Missing	11 (3.4)
Thrombotic Risk factor type	
Congenital only	5 (1.5)
Acquired only	241 (74.2)
Both congenital and acquired	19 (5.8)
None	60 (18.5)
Prior anticoagulant therapy	
No	191 (58.8)
Yes	134 (41.2)
Number of Medical Conditions	
<=2 comorbidities	223 (71.2)
> 2 comorbidities	41 (13.1)
None	49 (15.7)

Source: FDA reviewer's analysis

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

This was a retrospective study and fondaparinux exposure data was derived from CHLA's inpatient pharmacy records until the patient was discharged and then from pharmacy records and outpatient medical records.

Efficacy Results – Primary Endpoint

The primary efficacy endpoint was the proportion of patients with complete clot resolution at 3 months (±15 days). Among 325 patients in the efficacy analysis set, 146 (44.9%) achieved complete clot resolution of at least one clot, and 143 (44%) patients achieved complete clot resolution of all clots. In the primary analysis, the patients with missing outcome were considered as 'Not achieving Complete response', i.e., the missing data were considered as a 'Worst' outcome.

The subgroup analyses are included in the following tables below.

Table 10. Summary of Complete Clot Resolution by Age Group and Overall

Parameter	<2 years (N=30)	>=2 to <6 years (N=65)	>=6 to <12 years (N=78)	>=12 to <18 years (N=152)	Overall (N=325)
Complete resolution of at least one clot, n (%)	14 (46.7)	26 (40.0)	40 (51.3)	66 (43.4)	146 (44.9)
95% CI	(30.2, 63.9)	(29.0, 52.1)	(40.4, 62.1)	(35.8, 51.4)	(39.6, 50.4)
Complete Resolution of all clots, n (%)	14 (46.7)	25 (38.5)	39 (50.0)	65 (42.8)	143 (44.0)
95% CI	(30.2, 63.9)	(27.6, 50.6)	(39.2, 60.8)	(35.2, 50.7)	(38.7, 49.4)

Source: Applicant's Response to FDA information request

Table 11. Summary of Complete Clot Resolution by Weight Group and Overall

Parameter	<20 kg (N=95)	20-<40 kg (N=84)	40-<60 kg (N=72)	>=60 kg (N=73)	Overall (N=325)
Complete resolution of at least one clot, n (%)	42 (44.2)	45 (53.6)	30 (41.7)	28 (38.4)	146 (44.9)
95% CI	(34.6, 54.2)	(43.0, 63.8)	(31.0, 53.2)	(28.1, 49.8)	(39.6, 50.4)
Complete Resolution of all clots, n (%)	41 (43.2)	45 (53.6)	29 (40.3)	27 (37.0)	143 (44.0)
95% CI	(33.7, 53.2)	(43.0, 63.8)	(29.7, 51.8)	(26.8, 48.5)	(38.7, 49.4)

Source: Applicant's Response to FDA information request

Table 12. Summary of Complete Clot Resolution by [redacted] Group and Overall

Parameter	Female (N=167)	Male (N=158)	Overall (N=325)
Complete resolution of at least one clot, n (%)	76 (45.5)	70 (44.3)	146 (44.9)
95% CI	(38.1, 53.1)	(36.8, 52.1)	(39.6, 50.4)
Complete Resolution of all clots, n (%)	75 (44.9)	68 (43.0)	143 (44.0)
95% CI	(37.5, 52.5)	(35.6, 50.8)	(38.7, 49.4)

Source: FDA reviewer's analysis

Table 13. Summary of Complete Clot Resolution by Ethnic Group and Overall

Parameter	Hispanic or Latino (N=118)	Not Hispanic or Latino (N=120)	Unknown (N=87)	Overall (N=325)
Complete resolution of at least one clot, n (%)	57 (48.3)	52 (43.3)	37 (42.5)	146 (44.9)
95% CI	(39.5, 57.2)	(34.8, 52.3)	(32.7, 53.0)	(39.6, 50.4)

Parameter	Hispanic or Latino (N=118)	Not Hispanic or Latino (N=120)	Unknown (N=87)	Overall (N=325)
Complete Resolution of all clots, n (%)	55 (46.6)	52 (43.3)	36 (41.4)	143 (44.0)
95% CI	(37.8, 55.6)	(34.8, 52.3)	(31.6, 51.9)	(38.7, 49.4)

Source: FDA reviewer's analysis

There were no planned formal statistical tests. The primary efficacy results are consistent across groups.

Statistical reviewer comment: *The Applicant had "determined that 12 additional patients should have been included in the Efficacy Analysis Set" in their response to the FDA Information Request submitted on Aug 6, 2024. The analysis of the primary and secondary efficacy endpoints shown in the above tables included those 12 additional patients in the efficacy analysis set (N=325).*

Data Quality and Integrity

Data were provided electronically in standard data format, with SDTM and ADaM. SAS programs used to create key efficacy and safety outputs for the study were submitted along with the data. The Applicant also provided clear definition file for datasets and detailed analysis programs for assisting review. During the review, it was noted that there were errors in the Applicant's data collection in which 12 patients were erroneously omitted from the efficacy analysis and protocol deviation in collection of concomitant medications. The Applicant was asked to submit the updated data set for the re-analyses.

Efficacy Results – Secondary and other relevant endpoints

Proportion of patients with complete or partial clot resolution

Among 325 patients in the efficacy analysis set, 215 (66.2%) patients achieved complete or partial clot resolution of at least one clot of main VTEs up to Month 3, and 214 (65.8%) patients achieved complete or partial clot resolution of all clots of main VTEs up to Month 3. The subgroup analysis results are given in the following tables:

Table 14. Summary of Complete or Partial Clot Resolution by Age Group and Overall

Parameter	<2 years (N=30)	>=2 to <6 years (N=65)	>=6 to <12 years (N=78)	>=12 to <18 years (N=152)	Overall (N=325)
Complete or Partial resolution of at least one clot, n (%)	18 (60.0)	42 (64.6)	53 (67.9)	102 (67.1)	215 (66.2)

Parameter	<2 years (N=30)	>=2 to <6 years (N=65)	>=6 to <12 years (N=78)	>=12 to <18 years (N=152)	Overall (N=325)
95% CI	(42.3, 75.4)	(52.5, 75.1)	(57.0, 77.3)	(59.3, 74.1)	(60.8, 71.1)
Complete or Partial Resolution of all clots, n (%)	18 (60.0)	42 (64.6)	52 (66.7)	102 (67.1)	214 (65.8)
95% CI	(42.3, 75.4)	(52.5, 75.1)	(55.6, 76.1)	(59.3, 74.1)	(60.5, 70.8)

Source: FDA Reviewer's Analysis

Table 15. Summary of Complete or Partial Clot Resolution by Weight Group and Overall

Parameter	<20 kg (N=95)	20-<40 kg (N=84)	40-<60 kg (N=72)	>=60 kg (N=73)	Overall (N=325)
Complete or Partial resolution of at least one clot, n (%)	61 (64.2)	62 (73.8)	44 (61.1)	47 (64.4)	215 (66.2)
95% CI	(54.2, 73.1)	(63.5, 82.0)	(49.6, 71.5)	(52.9, 74.4)	(60.8, 71.1)
Complete or Partial Resolution of all clots, n (%)	61 (64.2)	62 (73.8)	43 (59.7)	47 (64.4)	214 (65.8)
95% CI	(54.2, 73.1)	(63.5, 82.0)	(48.2, 70.3)	(52.9, 74.4)	(60.5, 70.8)

Source: FDA reviewer's analysis

Of the 13 patients who had a PE at baseline, 3 patients had a follow-up assessment (2 patients at Week 1 and 1 patient at Month 1). The outcome of the follow-up was Stable Disease (Patient (b) (6)), Partial Resolution (Patient 248), and Complete Resolution (Patient (b) (6)). One patient (b) (6) had a follow-up assessment but the outcome was reported as "Unknown/Not Reported".

Dose/Dose Response

See section 7.2 of this review.

Durability of Response

Durability of response was not assessed in this retrospective review.

Persistence of Effect

Proportion of patients with VTE recurrence
Among the 325 patients in efficacy analysis set, 26 (8%) patients had clot recurrence up to 1 year, and 29 (8.9%) patients had clot recurrence at any time during the study.

Additional Analyses Conducted on the Individual Trial

Following the proposal to conduct a retrospective study (study 7001), on October 4, 2021, the Agency advised the Applicant that the study must include a literature based historical control to understand efficacy. The Applicant proposed a historical comparison of efficacy in terms of complete or partial clot resolution between the results from study 7001 and the results reported in the literature for LMWH products and DOACs in pediatric patients. The analysis below was based on the Applicant's original efficacy analysis set with 313 patients, as it did not include the additional 12 patients treated before 2008.

Specifically, the Applicant selected the following literature for comparison:

- Diab, Yaser A., et al. "IV versus subcutaneous enoxaparin in critically ill infants and children: comparison of dosing, anticoagulation quality, efficacy, and safety outcomes." Pediatric Critical Care Medicine 18.5 (2017): e207-e214.
- Halton, Jacqueline, et al. "Dabigatran etexilate for the treatment of acute venous thromboembolism in children (DIVERSITY): a randomised, controlled, open-label, phase 2b/3, non-inferiority trial." The Lancet Haematology 8.1 (2021): e22-e33.
- Ignjatovic, Vera, et al. "Dosing and monitoring of enoxaparin (low molecular weight heparin) therapy in children." British journal of haematology 149.5 (2010): 734-738.
- Klaassen, Irene LM, et al. "Are low-molecular-weight heparins safe and effective in children? A systematic review." Blood reviews 33 (2019): 33-42.
- Male, Christoph, et al. "Rivaroxaban compared with standard anticoagulants for the treatment of acute venous thromboembolism in children: a randomised, controlled, phase 3 trial." The Lancet Haematology 7.1 (2020): e18-e27.
- Warad, Deepti, et al. "A retrospective analysis of outcomes of dalteparin use in pediatric patients: a single institution experience." Thrombosis Research 136.2 (2015): 229-233.

The Applicant used the following methods for literature selection. For LMWH, the Applicant relied on the systematic review findings by Klassen et al. (2019), which looked at all published studies between 1980 and October 2017 concerning the dosage, safety, or efficacy of LMWH in neonates and children up to 19 years of age in Medline. The Applicant also cited a few clinical studies of commonly used LMWH in pediatric VTE patients with similar study design to their study. For DOACs, the Applicant included pivotal clinical studies of FDA-approved DOACs in pediatric VTE patients. The Applicant also checked some systematic reviews on DOACs, but no additional studies were deemed suitable for comparison.

Table 16. Complete Clot Resolution from Literature Review

Study ID	Author	Study Design	Drug	Route of Admin	Age	Number Assessed	Number Resolved	Percent Resolved	Lower 95% CI	Upper 95% CI
1	Diab	Retrospective	Enoxaparin	IV	<=3m	13	7	53.8	29.1	76.8

2	Diab	Retrospective	Enoxaparin	SC	<=3m	14	5	35.7	16.3	61.2
3	Diab	Retrospective	Enoxaparin	IV	>3m-4y	15	7	46.7	24.8	69.9
4	Diab	Retrospective	Enoxaparin	SC	>3m-2y	28	14	50.0	32.6	67.4
5	Halton	RCT	SoC	SC/PO	0-17y	90	38	42.2	32.5	52.5
6	Halton	RCT	Dabigatran	PO	0-17y	177	81	45.8	38.6	53.1
7	Ignjatovic	Retrospective	Enoxaparin	SC	0-16y	102	17	16.7	10.7	25.1
8	Klassen	Review	Various-LMWH	SC/IV	0-18y	806	266	33.0	29.8	36.3
9	Male	RCT	Rivaroxaban	PO	0-17y	335	128	38.2	33.2	43.5
10	Male	RCT	SoC	SC/IV/PO	0-17y	165	43	26.1	20.0	33.2
11	Warad	Retrospective	Dalteparin	SC	0-18y	42	34	81.0	66.7	90.0
	Combined #	All	All Drugs	SC/IV/PO	0-18y	1643	589	35.5	33.2	37.8
	Sponsor*	Retrospective	Fondaparinux	SC	0-17y	313	143	45.7	40.3	51.2
	Sponsor^	Retrospective	Fondaparinux	SC	0-17y	313	176	56.2	50.7	61.6

*Up to 3 months; ^At any time during the study; +Standard of Care
Combined literature results (does not include the Applicant's study) based on a fixed effect meta-analysis
Date Source: Applicant's response to information request.
Abbreviations: SoC: standard of care; IV: Intravenous; SC: Subcutaneous; PO: Per Os.

The above table lists the efficacy results of the historical trials (numbered 1 – 11). The Applicant also conducted a fixed effect meta-analysis that combines the 11 historical studies.

In the meta-analysis, the fixed-effect model (also known as the common effect model) assumes that the true response rate (θ) is same for all studies, and the observed differences in response rates are due to sampling error.Y_i denote the observed i.. The fixed effect model assumes that,

$$Y_i = \theta + \epsilon_i$$

where ϵ_i is the sampling error. Studies are weighted by the inverse of their within-study variance (i.e., more precise studies have a larger influence). This model is preferred when the studies are very similar in design, population, and methodology, and also the heterogeneity is minimal.

Another model for meta-analysis is the random effect model, which assumes that each study has its own true response rate, which follows a distribution around an overall mean. Specifically,

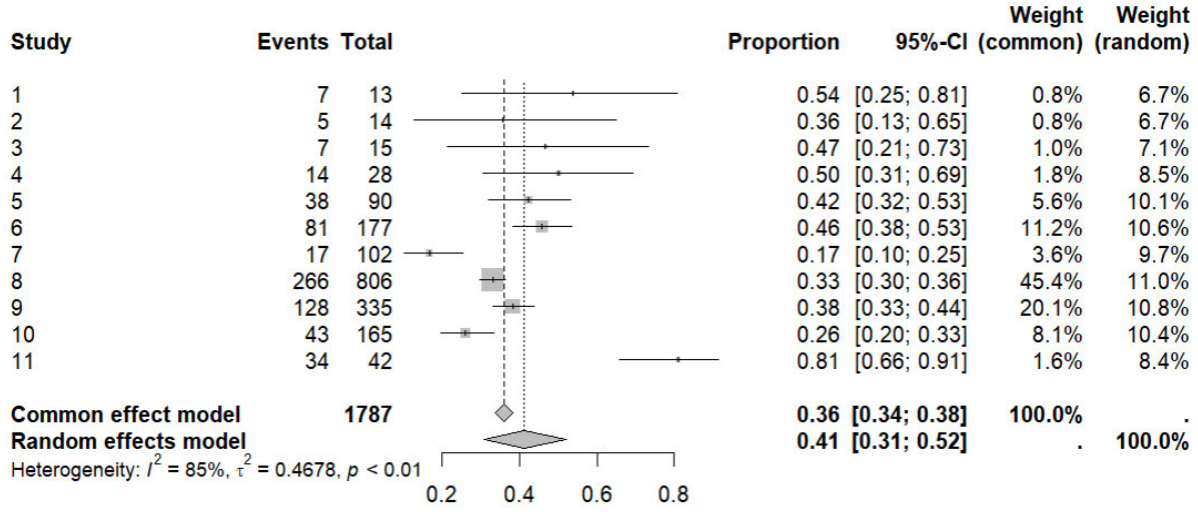
$$Y_i = \theta_i + \epsilon_i$$

where θ_i represents the response rate (random effect) for study i.. Studies are weighted by the inverse of the sum of within-study and between-study variance. As a result, smaller studies

contribute more weight than they do in a fixed-effect model. This model is preferred when studies have notable differences in design, populations, or methods, leading to heterogeneity.

The statistical reviewer conducted additional meta-analyses combining the 11 historical studies. The results are described below:

Figure 1. Plot: Meta-analysis of 11 Historical Studies



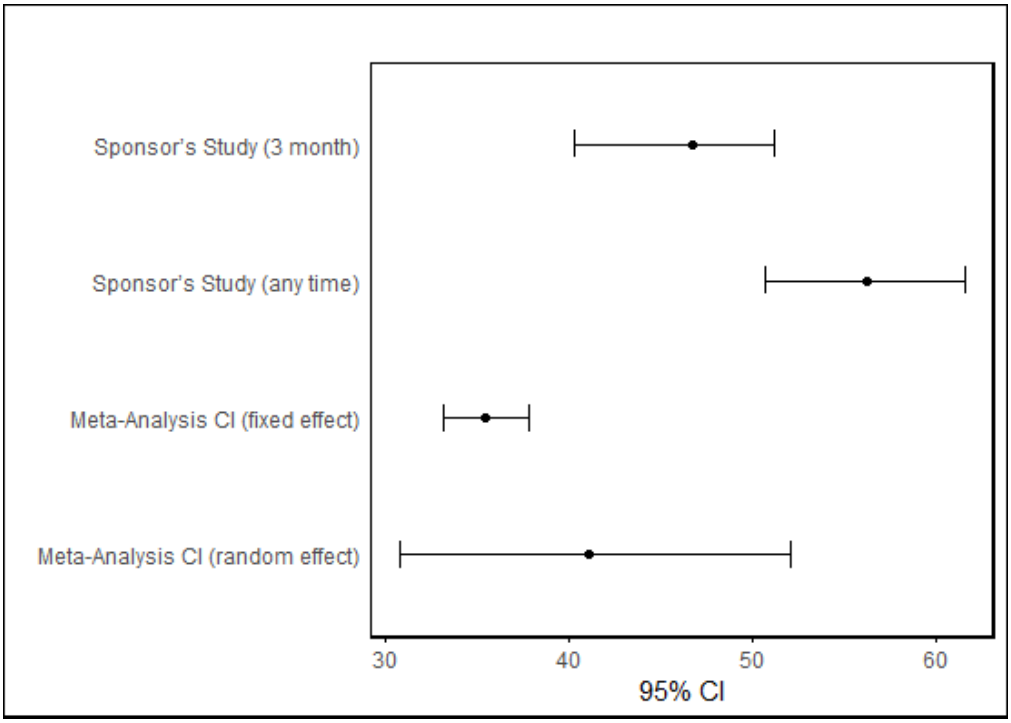
Source: FDA reviewer's analysis

Regarding heterogeneity:

- I^2=85%: This suggests that 85% of the total variation in the effect sizes is due to heterogeneity (differences between studies) rather than chance, indicating substantial heterogeneity.
- τ^2=0.4678: This is the estimated variance of the true effect sizes across studies, quantifying the heterogeneity. The value of 0.4678 quantifies this heterogeneity as moderate to high.
- p < 0.01, This indicates that the Cochran's Q-test for heterogeneity is statistically significant, meaning heterogeneity is unlikely to be due to random chance.

The results indicate substantial and statistically significant heterogeneity among those historical studies. Therefore, the random-effects model is more suitable than the fixed-effect model for the meta-analysis.

Figure 2. Plot: Complete Clot Resolution -- Comparison of Study 7001 and Meta-Analysis Results



Source: FDA reviewer's analysis

By comparing the Applicant's confidence intervals with that from a random effects meta-analysis, we conclude that the efficacy results from the Applicant's study in terms of complete clot resolution, align with results reported in the literature.

It is worth noting that combining clinical studies using meta-analysis has several limitations. Differences in study design, patient populations, and baseline characteristics can introduce significant heterogeneity. Publication bias and varying study quality may skew results. Limited availability of raw data or selective reporting of outcomes may hinder the comprehensiveness of the analysis. In addition, Klassen et al. (2019) combined the results of 19 studies, this includes data from some of the other literature included in the meta-analysis (e.g., Ignjatovic et al. 2010). The meta-analysis is purely descriptive.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

This section is not applicable to this review as the Applicant conducted a single, adequate and well controlled trial.

7.2. Dose and Dose-Response

1. Dose Selection for Study 7001

The approved fondaparinux dose in adult for the treatment of DVT and PE is 5 mg (body weight <50 kg), 7.5 mg (body weight 50 to 100 kg), or 10 mg (body weight >100 kg) by SC injection once daily.

The initial dose of 0.1 mg/kg once daily for fondaparinux in pediatric patients was selected based on a prospective pharmacokinetic and safety study conducted by Young et al. [5]. The data from this pilot study was also included in the submission. This pilot study aimed to determine the appropriate dose, dosing interval, pharmacokinetic profile, and safety of fondaparinux in children aged 1-18 years with DVT or HIT. The study enrolled 24 patients across three age cohorts and found that 0.1 mg/kg dosing resulted in pharmacokinetic profiles comparable to those in adults receiving standard dosing for VTE treatment. Due to safety considerations, the target peak fondaparinux level was set at 0.5-1 mg/L at 4 hours post-dose, which is lower than the mean peak level of 1.2-1.26 mg/L observed in adults. Pharmacokinetic modeling demonstrated that the 0.1 mg/kg once-daily dose in children achieved concentrations within the range that is known to be efficacious in adults. The study's findings supported the use of this dosing regimen, as 21 out of 24 patients achieved target peak concentrations after the first dose, and all 24 reached targets after no more than two dose adjustments.

Clinical Pharmacology reviewer comment: *From a clinical pharmacology perspective, the dose selection for Study 7001 is acceptable.*

2. Pharmacokinetic Results and Conclusion of Study 7001

The Study 7001 was a retrospective, single cohort study conducted in pediatric patients consecutively treated with fondaparinux at a single study center (CHLA). Detailed patient-level data of safety, efficacy, dosing, and peak fondaparinux blood concentrations for the eligible patients treated with at least one dose of fondaparinux were collected for most of the patients during the study period (2007-2018).

One of the primary objectives of study 7001 was to determine the proportion of pediatric patients achieving fondaparinux blood concentrations within a therapeutic range. This was based on peak blood concentrations achieved following the proposed initial dose of 0.1 mg/kg and a dose adjustment algorithm. It is important to note that fondaparinux levels were measured using an anti-Xa assay.

The table below shows the Applicant's summary of patients achieving therapeutic fondaparinux levels. Upon independent analysis, the reviewer confirmed these study results, noting only minor discrepancies from the Applicant's findings. The study results, derived from 336 patients in the PK dataset, demonstrated that with the current initial dose and dose adjustment algorithm, ~93% of patients reached the target therapeutic blood concentration of fondaparinux (0.5-1.0 mg/L). Only a small proportion of patients could not achieve therapeutic drug concentrations during the study, with ~3% of patients having subtherapeutic levels and ~5% experiencing supratherapeutic levels. To note, 2 patients experienced both subtherapeutic and supratherapeutic levels without achieving therapeutic level. The median time to reach therapeutic levels across all age groups was approximately 3 days, with an interquartile range of 2 to 6 days. Furthermore, age group analysis showed that patients achieving fondaparinux therapeutic concentrations was consistent across all age groups. This suggests that age does not impact the achievement of therapeutic drug concentrations when dosing is based on body weight in pediatric patients.

Table 17. Summary of Patients Achieving Fondaparinux Therapeutic Target Levels at Least Once During the Study

Fondaparinux Peak Concentration	<2 years (N=31)	≥2 to <6 years (N=64)	≥6 to <12 years (N=81)	≥12 to <18 years (N=160)	Overall (N=336)
Patients Achieving Therapeutic Target Levels At Least Once					
0.5 mg/L - 1 mg/L, n (%)	31 (100.0)	62 (96.9)	76 (93.8)	142 (88.8)	311 (92.6)
95% Confidence Interval	(88.8, 100.0)	(89.2, 99.6)	(86.2, 98.0)	(82.8, 93.2)	(89.2, 95.1)
Patients Not Achieving Therapeutic Target Levels *: Patients Achieving Subtherapeutic Levels					
<0.5 mg/L, n (%)	0 (0.0)	2 (3.1)	3 (3.7)	4 (2.5)	9 (2.7)
95% Confidence Interval	(0.0, 11.2)	(0.4, 10.8)	(0.8, 10.4)	(0.7, 6.3)	(1.2, 5.0)
Patients Achieving Supratherapeutic Levels					
>1 mg/L, n (%)	0 (0.0)	0 (0.0)	3 (3.7)	14 (8.8)	17 (5.1)
95% Confidence Interval	(0.0, 11.2)	(0.0, 5.6)	(0.8, 10.4)	(4.9, 14.2)	(3.0, 8.0)
Missing	-	-	-	1	1
Time to Achieve Initial Therapeutic Target Levels (0.5 mg/L - 1 mg/L) - Days					
n	31	62	76	142	311
Median	3.00	2.00	3.00	3.00	3.00
Mean (SD)	6.68 (9.662)	5.03 (11.835)	23.46 (69.845)	15.37 (78.692)	14.42 (63.855)
Q1-Q3	2.00 - 7.00	2.00 - 4.00	2.00 - 9.00	2.00 - 7.00	2.00 - 6.00
Min - Max	1.0 - 47.0	1.0 - 93.0	1.0 - 451.0	1.0 - 929.0	1.0 - 929.0
Patients Not Achieving Therapeutic Target Level At All	-	2	5	18	25

Peak fondaparinux levels at 3 hours post-dose were measured using a fondaparinux-based anti-Xa assay.
*Multiple nominations are possible.
Source: CSR of 7001, Table 22.

The table below shows the Applicant's summary of patients requiring fondaparinux dose adjustments. For patients who achieved therapeutic drug concentrations, approximately

55% of patients (reviewer calculated) did not require any dose adjustment to reach the therapeutic blood concentration of fondaparinux (0.5-1.0 mg/L) during their treatment course. This value is slightly lower than the applicant's reported 59.5%. This difference arises because of the inclusion of 14 patients in applicant's "No dose adjustment" category. Upon closer examination, these 14 patients never achieved therapeutic level during their study period.

Table 18. Summary of Patients Requiring Dose Adjustments for Fondaparinux

Characteristics	<2 years (N=31)	≥2 to <6 years (N=64)	≥6 to <12 years (N=81)	≥12 to <18 years (N=160)	Overall (N=336)
Number (%) of patients					
No dose adjustment	18 (58.1)	40 (62.5)	48 (59.3)	94 (58.8)	200 (59.5)
1 dose adjustment	7 (22.6)	10 (15.6)	19 (23.5)	30 (18.8)	66 (19.6)
2 dose adjustments	2 (6.5)	10 (15.6)	8 (9.9)	17 (10.6)	37 (11.0)
3 dose adjustments	1 (3.2)	1 (1.6)	1 (1.2)	10 (6.3)	13 (3.9)
4 dose adjustments	1 (3.2)	2 (3.1)	1 (1.2)	7 (4.4)	11 (3.3)
5 dose adjustments	1 (3.2)	-	2 (2.5)	2 (1.3)	5 (1.5)
More than 5 dose adjustments	1 (3.2)	1 (1.6)	2 (2.5)	-	4 (1.2)
Total Dose Adjustments Per Patient					
n	13	24	33	66	136
Median	1.00	2.00	1.00	2.00	2.00
Mean (SD)	2.23 (1.739)	1.96 (1.233)	2.30 (2.778)	2.00 (1.150)	2.09 (1.736)
Q1 - Q3	1.00 - 3.00	1.00 - 2.00	1.00 - 2.00	1.00 - 3.00	1.00 - 2.00
Min - Max	1.0 - 6.0	1.0 - 6.0	1.0 - 14.0	1.0 - 5.0	1.0 - 14.0
Total Number of Days Between Dose Adjustments Per Patient					
n	13	24	33	66	136
Median	9.00	6.67	14.00	6.50	7.63
Mean (SD)	139.40 (449.047)	17.90 (29.463)	41.60 (75.932)	23.00 (82.008)	37.74 (154.439)
Q1 - Q3	7.00 - 30.00	1.25 - 20.00	2.00 - 36.00	2.00 - 15.50	2.00 - 20.17
Min - Max	1.0 - 1633.0	0.0 - 121.0	1.0 - 306.0	1.0 - 660.0	0.0 - 1633.0
Total Number of Days of Dose Interruption Per Patient					
n	13	31	38	77	159
Median	0.00	0.00	0.00	0.00	0.00
Mean (SD)	0.46 (1.127)	69.58 (336.125)	30.00 (86.022)	45.45 (171.236)	42.79 (193.959)
Q1 - Q3	0.00 - 0.00	0.00 - 2.00	0.00 - 0.00	0.00 - 1.00	0.00 - 1.00
Min - Max	0.0 - 4.0	0.0 - 1874.0	0.0 - 366.0	0.0 - 1051.0	0.0 - 1874.0

Source: CSR of 7001, Table 23.

Clinical Pharmacology reviewer assessment:

The PK analysis shows the following key findings:

1. Approximately 55% of patients achieved therapeutic blood concentrations (0.5-1.0 mg/L) without any dose adjustments.
2. Over 90% of patients reached the target therapeutic blood concentration with the initial dose and subsequent adjustments.
3. The median time to reach therapeutic levels across all age groups was approximately 3 days.

4. Attainment of therapeutic concentrations was consistent across all age groups, suggesting no significant age-related impact when dosing is based on body weight.

Conclusion
Based on the above key findings, the weight-based dosing approach, utilizing an initial dose of 0.1 mg/kg fondaparinux in conjunction with the proposed dose adjustment algorithm, demonstrated the ability in achieving and maintaining therapeutic blood concentrations in pediatric patients treated with fondaparinux. The high percentage of patients reaching target levels, coupled with the consistency across age groups, supports the appropriateness of this dosing strategy.

Therefore, we conclude that the proposed weight-based dosing approach and adjustment algorithm for fondaparinux are acceptable for use in the pediatric population.

The only caveats to note is that renal function of patients enrolled in the retrospective chart study was not available. It is known that fondaparinux is renally eliminated and there is potential for higher exposures in patients with renal impairment. Due to lack of information, the review team is unable to provide dosing instructions in pediatric patients with renal impairment and recommend that the use be avoided in such patients due to concerns for higher exposures.

3. Discussion of minor issues not affecting the overall conclusion

A. Minor Discrepancies in Dose Adjustment Classification:
Based on the reviewer's analysis, 14 patients with fondaparinux level (measured by anti-Xa assay) outside the therapeutic range did not have any recorded dose adjustment. The specific patient numbers and their corresponding fondaparinux levels are presented in Table X.

Table 19. List of Patients with No Dose-adjustment Outside the Therapeutic Range

Patients	Anti-Xa level (unit: mg/L)	Treatment Duration
(b) (6)	1.14	96
	1.09	27
	0.49	1
	1.07	2
	1.07	6
	1.04	1
	1.08	9
	1.16	2
	1.02	2

Patients	Anti-Xa level (unit: mg/L)	Treatment Duration
(b) (6)	1.01	1
	1.65	1
	0.44	1
	0.02	3
	0.43	4

Source: Reviewer generated

A further examination of the patients revealed that only 5 patients were treated over 4 days, while 9 out of 14 had very short treatment durations (≤3 days), which may have limited their opportunities for appropriate dose adjustments. The misclassification of these results leads to inaccuracies in the reported rates of patients who did not require dose adjustments to reach therapeutic concentrations. The Applicant reported a rate of 59.5% (200 out of 336), while the reviewer's recalculated rate is 55.4% (186 out of 336). Despite of this discrepancy in classification, the overall proportion of patients achieving therapeutic drug concentrations remains high, which exceeds 90% of the total population. Therefore, the impact of this discrepancy to overall conclusion is limited.

B. Timing of First Concentration Measurement:

According to the study protocol, fondaparinux levels were measured 3 hours after the second or third dose (Day 2 or Day 3) following the start of treatment. Typically drug levels for dose adjustment are measured at steady state and fondaparinux having a half-life of 17 to 21 hours, reaches steady state by Day 4 or 5. Measuring the levels before achieving steady state, on Day 2 or 3, is also reasonable because the levels at Day 2 are expected to be only approximately 30% lower than the steady state. The dose adjustment algorithm in pediatric patients is primarily designed to reduce the risk of overshooting into supratherapeutic levels by monitoring early and to gradually titrate doses in smaller increments to the therapeutic range.

Table 20. Summary of the Time for 1st Fondaparinux Level* Measurement

1st PK Measurement	Day 1	Day 2	Day 3	Day 4	Day>=5
Number of Patients	35	184	67	11	39

*Measured by the Anti-Xa level
Source: Clinical Pharmacology Reviewer

C. Body Weight Considerations:

The study utilized a weight-based dosing approach for fondaparinux, with initial dosing at 0.1 mg/kg and subsequent dose adjustments also based on weight. However, a limitation of the

study was the use of a constant body weight for each patient throughout the treatment period, which in some cases extended beyond 900 days. This fixed weight assumption may have resulted in potential under- or over-dosing, particularly for patients with significant weight changes over the extended treatment duration.

Despite this limitation, the clinical impact of using a constant weight appears to be limited. The study results demonstrate that the majority of patients achieved and maintained therapeutic drug concentrations with the implemented dose adjustment algorithm. In addition, the dose of fondaparinux is adjusted based on anti-Xa level therefore, weight is expected to have minimal impact on achieving a therapeutic dose.

7.3. Additional Efficacy Considerations

7.3.1. Considerations on Benefit in the Postmarket Setting

One limitation of this study is it was conducted at single center, CHLA. However, CHLA is a large tertiary hospital and while the demographic data is lacking in terms of ethnicity, this hospital typically cares for a variety of patients with ethnic and socioeconomic backgrounds. In addition, pediatric VTE is typically managed by pediatric hematologists, therefore, management will likely by similar to how patients were managed at CHLA. It is reasonable to expect that efficacy results would be similar in the post marketing setting.

7.3.2. Other Relevant Benefits

An added benefit of Arixtra is the once daily SC dosing that can be monitored for safety and efficacy with following anti-Xa levels. LMWHs typically are administered twice daily.

7.4. Integrated Assessment of Effectiveness

Study 7001 was a retrospective study conducted in pediatric patients less than 18 years of age treated with at least one dose of fondaparinux injection at a single center. Per CHLA institutional practice, fondaparinux levels were monitored after the second or third dose of fondaparinux until therapeutic levels were achieved. Fondaparinux levels were then monitored weekly while patients were admitted within the hospital and, approximately every 1-3 months while outpatient for the duration of treatment. Dosing adjustments were made to achieve peak fondaparinux blood concentration within the therapeutic target of 0.5-1.0 mg/L.

In total, 325 pediatric patients between the age of 0.5-17 years had a diagnosis of VTE and treated with at least one dose of fondaparinux (Arixtra or generic product).

The efficacy of fondaparinux was based on measuring the proportion of pediatric patients with complete clot resolution up to 3 months (±15 days). Among 325 patients in the efficacy analysis

set, 44.9% (95% CI: 39.6, 50.4) achieved complete clot resolution of at least one clot, and 44% (95% CI: 38.7, 49.4) patients achieved complete clot resolution of all clots. Efficacy results were consistent across pediatric age and weight groups. The efficacy results from Study 7001 in terms of complete clot resolution following treatment with fondaparinux, align with rates of complete clot resolution following treatment with standard of care anticoagulants (i.e., LWMH, DOACs) reported in the literature. Further, the high percentage of patients reaching target levels, coupled with the consistency across age groups, supports the appropriateness of this dosing strategy.

Confirmatory evidence of efficacy is provided by prior approvals of the prophylaxis and treatment of VTE in the adult population. There are several adequate and well controlled studies conducted in adults to support a variety of indications, see Section 3.1 for a complete list of approved indications. While the etiology of VTE in pediatric and adult patients differ, the pathophysiology of clot formation and clinical outcomes (i.e., clot progression, risk of PE, PTS etc.) are the same. Therefore, it is reasonable to extrapolate efficacy from the adult population. This approach has been used with other anticoagulants approved for pediatric patients. In summary, the study results support expanding the indication of treatment of VTE to pediatric patients and are further supported by the literature and adult experience with fondaparinux.

8. Review of Safety

8.1. Safety Review Approach

The review of safety was based upon:

- Clinical Study Report for 7001
- Protocol for 7001
- Patient narratives
- Case report forms
- Datasets

Case report forms and narratives were provided by the Applicant and reviewed for adverse events of special interest (AESI), and deaths that occurred in the safety population.

Clinical reviewer comment: *The Applicant identified 366 patients evaluable for safety analysis in study 7001. As noted in section 3.1, on December 13, 2021, the Applicant agreed to include all patients who received fondaparinux in the safety analysis set, including patients who received fondaparinux prior to 2008. However, the reviewer noted that patients treated with fondaparinux prior to 2008 were not included in datasets for review. In response to the Agency information request (April 19, 2024) and after assessing data prior to 2008, the Applicant clarified that they only included nine of the original 24 FondaKIDS study* patients *in Study 7001. The Applicant stated the other 15 patients were excluded from Study 7001 for the following*

reasons:

- *8 patients were enrolled from institutions other than CHLA.*
- *7 patients received Arixtra from the investigational pharmacy during their time in FondaKIDS and either*
    - *discontinued Arixtra by Day 21 (per the FondaKIDS study design)*
    - *if they continued, they received it [subsequent doses] from a pharmacy other than CHLA*
    - *Did not continue to receive care at CHLA*

On May 30, 2024, per the Agency request, the Applicant provided CRFs and SDTM datasets for the seven patients (Patients (b) (6) *) that received Arixtra from the investigational pharmacy. Upon review, the Agency had further questions which led the Applicant to notice errors in the data extraction of all seven patients' data submitted on May 30, 2024 (Supporting Document Number (SDN) 792). The Applicant then conducted 100% source data verification of the seven patients' data resulting in changes to all seven patients' CRFs and all but two datasets provided in their earlier submission (SDN 792). Table 27 provides details of the patient disposition for the seven patients not included in Study 7001 who, based on Agency review, met eligibility criteria and should have been included. The Agency evaluated the seven patients who received fondaparinux from the investigational pharmacy in the safety analysis. It was reasonable not to include the 8 patients treated at other institutions given the protocol only specified to include patients treated at CHLA.*

8.2. Review of the Safety Database

8.2.1. Overall Exposure

In total, 366 patients were exposed to fondaparinux at CHLA through December 31, 2018. Patients received fondaparinux for a median duration of 85 days (range: 1-3768). A total of 198 patients were exposed to fondaparinux <3 months, 105 patients were administered fondaparinux ≥3 to <6 months, 45 patients received fondaparinux ≥6 to <12 months, and 18 patients received fondaparinux for 12 months or longer.

Clinical reviewer comment: *The body weight categories used to actually dose patients as described in the protocol and the body weight categories used to analyze patients are slightly different. Patients who weighed 10 to 20 kg were initially dosed 0.1 mg/kg and rounded to the nearest 0.1 mg (dose was prepared by the pharmacist) while patients weighing >20 kg were initially dosed by prefilled syringes based on weight ranges of >20 to 40 kg: 2.5 mg prefilled syringe, >40 to 60 kg: 5 mg prefilled syringe, and >60 kg: 7.5mg prefilled syringe. The categories used in the datasets for analysis are the following: <20 kg, 20- <40kg, 40-<60 kg, and ≥60 kg. See* Table 21 *below. Dataset were searched specifically for patients who would have the potential to be miss-dosed based on weights of 20, 40, or 60 kg. Four patients weighing either*

20 kg or 40 kg were identified who were dosed differently than specified in the protocol. There were only very minor differences (4 patients) between the protocol specified dosing categories vs the categories used in datasets, therefore there is minimal impact to the assessment of safety.

Table 21. Number of Patients Analyzed Based on Categorization of Baseline Body Weight

Baseline Body Weight (kg) Category Used for Dosing	N=366 n (%)	Baseline Body Weight (kg) Category Used for Data Analysis	N=366 n (%)
10-20	109 (29.8)	<20	107 (29.2)
>20-40	91 (24.9)	20-<40	91 (24.9)
>40-60	88 (24)	40-<60	90 (24.6)
>60	77 (21)	≥60	77 (21)

Source: FDA Analysis

When considering the dosing weight category used to analyze data, two patients in the 20-<40 kg category, each weighing 20 kg, should have both been dosed with the pharmacist prepared dose of 0.1 mg/kg exactly (2 mg). However, one patient was dosed with 1.5 mg and the other with 2.5 mg (patients (b) (6)*, respectively). Two other patients (* (b) (6)*) should have both received the 2.5 mg prefilled syringes. Instead, they received initial doses of 5 mg and 4 mg, respectively, but were included in the baseline weight category of 40-<60 kg which was to receive the 5 mg prefilled syringes. See* Table 22 *below. No safety or efficacy issues occurred in the two patients that received a higher dose of fondaparinux.*

Table 22. Differences in Dosing Based on Body Weight Category

Patient Number	Patient Baseline Weight	Initial Dose Based on Dosing Weight Category Used for Data Analysis	Actual Dose Given
(b) (6)	20 kg	2 mg	1.5 mg
	20 kg	2 mg	2.5 mg
	40 kg	2.5 mg	5 mg
	40 kg	2.5 mg	4 mg

Source: FDA Analysis

8.2.2. Relevant characteristics of the safety population:

The safety population consisted of 366 patients who received at least one dose of fondaparinux at CHLA through December 31, 2018. This differed from the efficacy population who, in addition, had documentation of a VTE. Demographic and baseline disease characteristic data are shown in the tables below. Of note, at CHLA, patients may have reported their race as "other," but they were not required to specify it. Of the 176 patients whose race was reported as "other," 113 patients' race was listed as unknown, 47 patients' race was specified as Latina/Hispanic, 14 patients' race was specified as other/white, 1 patient's race was specified as Armenian, and 1 patient's race was specified as was Natural (Native) American. Patients were also permitted to decline providing their race. In these cases, race was reported as "Unknown/Missing."

Table 23. Demographic Information for Patients in 7001 Safety Analysis Population

Safety Analysis Population	
Variable	Fondaparinux (N= 366) n (%)
Sex	
Female	187 (51)
Male	179 (49)
Race	
White	84 (23)
Black or African American	28 (8)
Asian	23 (6)
Native Hawaiian or Other Pacific Islander	1 (0.3)
Unknown	54 (15)
Other	176 (48)
Ethnicity	
Hispanic/Latino	140 (38)
Not Hispanic/Latino	126 (34)
Unknown/Missing	100 (27)
Age (years)	
< 2 years	35 (10)
≥ 2 to < 6 years	71 (19)
≥ 6 to < 12 years	88 (24)
≥ 12 to < 18 years	172 (47)
Baseline Body Weight	
< 20 kg	107 (29)

Safety Analysis Population	
Variable	Fondaparinux (N= 366) n (%)
20 - <40 kg	91 (25)
40 - <60 kg	90 (25)
≥ 60 kg	77 (21)

Source: Applicant's CSR

Table 24. Baseline Disease Characteristics

Baseline Disease Characteristics	
Variable	Fondaparinux (N= 366) n (%)
Number of VTEs	
<2	287 (78)
≥2	38 (10)
Missing	41 (11)
Location of VTEs	
Upper extremity (right)	95 (26)
Upper extremity (left)	99 (27)
Lower extremity (right)	42 (11.5)
Lower extremity (left)	44 (12)
Cerebral sinus	22 (6)
Superior vena cava	2 (0.5)
Inferior vena cava	6 (1.6)
Pulmonary embolism	13 (3.6)
Other	45 (12.3)
Unknown/not reported	7 (1.9)
Missing	41 (11.2)
No VTE at baseline	8 (2.2)
Time since diagnosis of VTEs (days)	
Median (range)	2 (0-164)
Risk factor type	
Both congenital and acquired	21 (5.7)
Congenital only	8 (2)
Factor V Leiden	15 (4.1)
Prothrombin mutation	3 (0.8)
High homocysteine levels	1 (0.3)

Baseline Disease Characteristics	
Variable	Fondaparinux (N= 366) n (%)
Antithrombin III deficiency	3 (0.8)
Protein C deficiency	3 (0.8)
Protein S deficiency	4 (1.1)
Elevated factor VIII levels	6 (1.6)
Other	222 (60.7)
Unknown/Not reported	32 (8.7)
Acquired only	255 (70)
Antiphospholipid antibodies	12 (3.3)
Heparin-induced thrombocytopenia	2 (0.5)
Nephrotic syndrome	3 (0.8)
Estrogen-containing hormonal contraceptives	9 (2.5)
Myeloproliferative disorders	1 (0.3)
Cancer or malignancies	124 (33.9)
Obesity (BMI >95% for age)	16 (4.4)
Catheter Related Thrombosis	179 (48.9)
Orthopedic surgery	16 (4.4)
Other	33 (9)
None	82 (22.4)
Prior anticoagulant therapy	
No	214 (59)
Concomitant anticoagulant	
Enoxaparin	30 (8)
Warfarin	25 (7)

Source: Applicant's CSR

Clinical reviewer comment: *The safety database represents a patient population consistent with the patient demographics and disease characteristics of pediatric patients with VTE.*

8.2.3. Adequacy of the safety database:

In Study 7001, 366 patients were exposed to fondaparinux.

Clinical reviewer comment: *The safety database is adequate for assessing the safety of fondaparinux in pediatric patients with VTE.*

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

The safety data submitted was well organized and easily identified. The Applicant provided all clinical datasets. The Applicant also provided narratives for all patients resulting in death, major bleeding events, non-major bleeding events, minor bleeding events, and AESI leading to drug withdrawal. Clinical laboratory data for safety parameters, data for vital signs, physical examinations, and other safety observations were not collected for this retrospective study. Overall, the submission quality regarding the safety population was adequate.

8.3.2. Categorization of Adverse Events

Adverse event collection in this retrospective study was limited to bleeding events and AESIs (anemia, allergic reactions, abnormal liver function tests, localized and generalized skin-associated events, and events of thrombocytopenia, hypokalemia, and decreased blood pressure and hypotension.) The AESIs were selected if they were adverse reactions reported in clinical trials or are potentially serious events seen in post-marketing for fondaparinux. An AE was considered treatment-emergent if the event's onset date was on or after the start date of fondaparinux. Only events which started or worsened on or after the start date of fondaparinux were analyzed. AEs were not specifically elicited in this retrospective study nor were they graded to assess severity. SAEs were not collected. Follow up documentation was based on documentation in the medical chart and extraction if the AE was determined to be prespecified. Adverse events were assessed by frequency.

Clinical reviewer comment: *The Applicant collected important data regarding safety of fondaparinux use in pediatric patients based on concerns for bleeding and events observed historically with product use. The lack of captured information for safety observations and lab assessments is a limitation of this safety analysis. The Agency queried the Applicant if all adverse events could be extracted, but the Applicant stated it would not be possible to interpret adverse events given underlying disease comorbidities in this complex and heterogenous population. Therefore, to further understand the safety profile of fondaparinux in pediatric patients the clinical reviewer reviewed FAERS database, literature and the Applicant's global safety database for any safety signal.*

8.3.3. Routine Clinical Tests

Routine clinical tests were obtained per standard medical care and were not captured in this retrospective study unless they were identified as an AESI. Although anemia, thrombocytopenia, hypokalemia, and liver function abnormalities were collected as descriptive AESIs these were not based on prespecified numerical values. During review, the Agency requested platelet count measurements for patients with bleeding events to further understand drug attribution.

8.4. Safety Results

8.4.1. Deaths

In Study 7001, a total of 32 patient deaths were reported in the Safety Analysis Set, which includes deaths that occurred more than 30 days after the last dose of fondaparinux. The most common causes of death were respiratory failure, leukemia, septic shock, and multi-system organ failure.

Of the 32 deaths, 12 deaths (3.3%) occurred (see Table 25) while patients were receiving fondaparinux and up to 30 days after last dose of drug. One patient (patient (b) (6)) died due to severe thrombosis of the hepatic veins due to Budd-Chiari syndrome and subsequent liver and multi-organ failure. The patient narrative is provided below.

Patient (b) (6) was a 17-year-old Black or African American female with Budd-Chiari syndrome and inflammatory bowel disease who experienced hepatic infarction, liver failure and subsequent multi-system organ failure and death. Prior medications included heparin and enoxaparin. She was receiving numerous concomitant medications at the time of death. A VTE was identified by computed tomography (CT) of the abdomen and pelvis demonstrating thrombosis of hepatic veins. Cardiac CT showed multiple foci in the paraseptal left ventricle and right ventricle outlet walls suggestive of mural thrombi, and multiple acute pulmonary emboli of the left lower lobe. The patient received six doses of fondaparinux then transitioned to another anticoagulant. On Day 12 the patient died due to severe thrombi in her hepatic veins consistent with Budd-Chiari syndrome which led to hepatic infarction and liver failure. The primary cause of death was reported to be multi-system organ failure.

Table 25. Patient Listing of Deaths Occurring On-Treatment and up to 30 Days After the Last Dose of Fondaparinux

Patient ID	Cause of Death
(b) (6)	Multiple complex issues including infection, sepsis, multiorgan dysfunction, worsening HLH, hypotension, ARDS
	Relapsed T-cell leukemia, aspergillus infection, kidney failure and cardiorespiratory failure
	Gram negative septic shock
	Shock and multisystem organ failure
	Pseudomonas pneumonia
	Metastatic rhabdomyosarcoma
	Pseudomonas pneumonia progressing to septic shock and multiorgan failure
	Multi-organ failure as a result of leukemia associated with a cardiac thrombus and Loeffler's myocarditis leading to systemic inflammatory response syndrome.
	Budd-Chiari syndrome leading to hepatic infarction, liver, and multi-system

Patient ID	Cause of Death
	organ failure
(b) (6)	Multi-organ failure due to ethylmalonic encephalopathy
	Respiratory failure due to chronic lung disease
	Renal failure and disseminated candida infection and typhlitis secondary to chemotherapy-induced neutropenia

Source: Clinical Reviewer
Abbreviations: HLH, hemophagocytic lymphohistiocytosis; ARDS, acute respiratory distress syndrome

Clinical reviewer comment: *The patient population included this study was complex with serious underlying diseases or significant comorbidities. Most deaths were related to the underlying disease or complications due to treatments for these conditions. No patients died due to bleeding, while on-treatment with fondaparinux or up to 30-days after its discontinuation. One patient* (b) (6) *died due to liver failure and multi-organ failure related to Budd-Chiari syndrome (severe liver thromboses). This was the only thrombosis-related death to occur.*

8.4.2. Serious Adverse Events

Adverse events were not categorized as serious.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Major Bleeding Events
Major bleeding events resulted in the interruption of fondaparinux treatment for 4 patients (Patients (b) (6) and the discontinuation of fondaparinux for 3 patients (Patients (b) (6). Patient (b) (6) had major bleeding that was retroperitoneal, pulmonary, intracranial, or otherwise involved the CNS; patients (b) (6) had major bleeding that required surgical intervention in an operating suite. All major bleeding events that lead to discontinuation of fondaparinux treatment were reported in patients between the ages of ≥2 to <12 years.

Non-Major Bleeding Events
Treatment with fondaparinux was interrupted in 7 patients (1.9%), and fondaparinux was discontinued in 4 patients (1.1%) due to non-major bleeding events. Two patients (Patients (b) (6)) had events of clinically overt bleeding necessitating a blood product to be administered and two patients (Patients (b) (6)) had bleeding events that required surgical intervention not in an operating room to restore hemostasis. All non-major bleeding events that led to discontinuation of fondaparinux treatment were reported in patients between the ages of ≥6 to <18 years.

AESIs

In total, 4 patients (1.1%) discontinued fondaparinux due to an AESI. One patient each had thrombocytopenia (Patient (b) (6) allergic reactions (Patient (b) (6), hypokalemia (Patient (b) (6), and decreased blood pressure and hypotension (Patient (b) (6) Two patients (Patients (b) (6) and (b) (6) had local and generalized skin-associated events.

8.4.4. Significant Adverse Events

Not applicable. Severity of adverse events were not assessed.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Of the 366 patients in the study, 193 patients (52.7%) had AESIs. The most common AESI was anemia [101 patients (27.6%)], followed by events of thrombocytopenia [66 patients (18%)], abnormal liver function tests [58 patients (15.8%)] hypokalemia [53 patients (14.5%)], decreased blood pressure and hypotension [21 patients (5.7%)] and allergic reaction [5 patients (1.4%)]. The overall incidence of AESI was comparable across the age groups. See table below.

Table 26. Summary of Adverse Events of Special Interest (SAF)

AESI	<2 yrs (N=35) n (%)	≥2 to <6 yrs (N=71) n (%)	≥6 to <12 yrs (N=88) n (%)	≥12 to <18 yrs (N=172) n (%)	Overall (N=366) n (%)
Any AESIs	19 (54.3)	43 (60.6)	40 (45.5)	91 (52.9)	193 (52.7)
Anemia	10 (28.6)	24 (33.8)	22 (25)	45 (26.2)	101 (27.6)
Thrombocytopenia	4 (11.4)	7 (9.9)	17 (19.3)	38 (22.1)	66 (18)
Abnormal Liver Function tests	5 (14.3)	12 (16.9)	12 (13.6)	29 (16.9)	58 (15.8)
Hypokalemia	5 (14.3)	11 (15.5)	12 (13.6)	25 (14.5)	53 (14.5)
Decreased Blood Pressure and Hypotension	1 (2.9)	3 (4.2)	4 (4.5)	13 (7.6)	21 (5.7)
Allergic Reaction	2 (5.7)	0 (0)	2 (2.3)	1 (0.6)	5 (1.4)

Source: Clinical reviewer

Clinical reviewer comment: *The Applicant excluded 7 patients from the study that received fondaparinux from the investigational pharmacy. Disposition for these 7 patients are outlined below. Five of the 7 patients experienced AEs including major bleeding, clinically relevant non-major bleeding, AESIs and discontinuation of fondaparinux due to AEs (see table below). No new safety signal was identified after reviewing the 7 patients who received fondaparinux from the investigational pharmacy.*

Table 27. Seven Patients who Participated in FondaKIDS and Received Fondaparinux from Investigational Pharmacy

Patient number	Exposure to Fondaparinux	Prescence of VTE	Reason for Fondaparinux Discontinuation
[redacted]	(b) (6)	Diagnosed with VTE (b) (6) and persistent VTE on (b) (6)	Drug interrupted for AE of bleeding, clinically relevant non-major bleeding (blood in stool). Then drug discontinued for AE of bleeding, clinically relevant non-major bleeding (blood in stool).
		Diagnosed with VTE (b) (6)	Change to alternative: coumadin
		Diagnosed with VTE (b) (6) different location	AESI of rash/ urticaria/allergic reaction moderate in severity and probably related to fondaparinux.
		Diagnosed with VT (b) (6) diagnosed with VTE of different location.	Major bleeding: bleeding that is retroperitoneal, pulmonary, intracranial, or otherwise involves the central nervous system. AESI: abnormal liver function tests
		Diagnosed with VTE (b) (6)	AE, epistaxis x2, any overt or macroscopic evidence of bleeding that does not fulfill criteria for either major bleeding or clinically relevant, nonmajor bleeding
		Diagnosed with VTE (b) (6)	Patient decision
		Diagnosed with VTE (b) (6)	Drug interruption for AESI, local and generalized skin-associated events (thought due to vancomycin). Experienced AESI of anemia and action taken unknown. Experienced decreased blood pressure and hypotension and action taken not applicable as dose was already interrupted

Source: Clinical Reviewer
Abbreviations: AESI, adverse event of special interest; AE, adverse event; VTE, venous thromboembolism

8.4.6. Laboratory Findings

Laboratory test data was not collected.

8.4.7. Vital Signs

Vital signs were not collected.

8.4.8. Electrocardiograms (ECGs)

ECG data was not collected.

8.4.9. QT

There were no QT studies in this submission.

8.4.10. Immunogenicity

Immunogenicity data was not collected in this submission.

8.5. Analysis of Submission-Specific Safety Issues

8.5.1. Bleeding

Major bleeding events, defined as per the ISTH criteria, was the primary safety outcome of interest in this study. In Study 7001 (N=366), 19 patients (5.2%) experienced a composite major bleeding event (n=7) or clinically relevant nonmajor bleeding event (n=12) (see table below). Three patients discontinued fondaparinux because of bleeding events (see Section 8.4.3). No patient had a fatal bleeding event. The day of onset of the major events was between 7 to 91 days. All major bleeding events were reported in patients aged ≥2 to <18 years. Underlying medical conditions (i.e., systemic lupus erythematosus, Wilms tumor, antiphospholipid syndrome, or indwelling chest tube) all of which may have increased risk of bleeding.

Table 28. Major and Clinically Relevant Nonmajor Bleeding in Study 7001

Bleeding Adverse Events	**N= 366 n (%)**
Major Bleeding	**7 (1.9)**
Fatal Bleed	0 (0)
Bleeding that is retroperitoneal, pulmonary, intracranial, or otherwise involves the CNS	3 (0.8)
Bleeding that requires surgical intervention in an operating suite	3 (0.8)
Clinically overt bleeding associated with a decrease in Hgb of at least 20 g/L (2g/dL) in a 24-h period	1 (0.3)

Bleeding Adverse Events	**N= 366 n (%)**
Clinically Relevant Nonmajor Bleeding	**11 (3.0)**
Overt bleeding for which a blood product is administered, and which is not directly attributable to the patient's underlying medical condition	8 (2.2)
Bleeding that requires medical or surgical intervention to restore hemostasis, other than in an operating room	4 (1.1)

Source: Clinical Reviewer

One patient was identified to have bleeding following a supratherapeutic level. Patient (b) (6) was a 10-year-old, 41 kg, Asian, male who developed bleeding that required surgical intervention (severe chest tube bleeding) on (b) (6) The patient received his initial dose of fondaparinux on Day 1 (b) (6) and last dose (b) (6) (level 0.41) when he was taken to OR. The patient had two supratherapeutic levels (b) (6) (1.24) and (b) (6) (1.03) with no dose adjustments.

Eleven patients (3%) had non-major bleeding events: 8 patients (2.2%) had overt bleeding for which a blood product was administered, and which was not directly attributable to the patient's underlying medical condition and 4 patients (1.1%) had bleeding that required medical or surgical intervention to restore hemostasis other than in an operating room. All non-major bleeding events warranted either interruption or withdrawal of fondaparinux injection treatment except for 1 patient for whom the action taken with fondaparinux was not reported. All non-major bleeding events were reported in patients between the ages of ≥2 to <18 years.

Overall, 65 patients (17.8%) had composite minor bleeding events: 64 patients (17.5%) had overt or macroscopic evidence of bleeding that did not fulfill the criteria for either major bleeding or clinically relevant, non-major bleeding and one patient (0.3%) had non-major menstrual bleeding resulted in a medical consultation and/or intervention.

8.5.2. Post-Thrombotic Syndrome (PTS)

Overall, 6 (1.6%) patients experienced treatment-emergent PTS, which included leg pain (patients (b) (6)), leg heaviness (patients (b) (6)), edema (patients (b) (6)) and skin pigmentation (patients (b) (6) in two patients (0.5%) each. Patient (b) (6) experienced more than one PTS related sign and symptom (edema, leg heaviness, leg pain, and skin pigmentation). Patient (b) (6) experienced other PTS (venous congestion in right groin, right upper thigh, and lower abdomen). Patient (b) (6) also experienced other PTS (venous stasis ulcer) during the study period. All PTS events were reported in patients between the ages of ≥2 to <18 years.

8.6. Safety Analyses by Demographic Subgroups

Age, [redacted] and race subgroups were too small to make meaningful safety comparisons.

8.7. Specific Safety Studies/Clinical Trials

No specific study or clinical trial was conducted to evaluate a specific safety concern for this review.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

No human carcinogenicity studies were conducted with this submission.

8.8.2. Human Reproduction and Pregnancy

There were no additional evaluations conducted in the studies included in this application.

8.8.3. Pediatrics and Assessment of Effects on Growth

There were no specific studies conducted on the effect of fondaparinux on growth or bone metabolism.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Risk of medication errors is discussed in Section 8.9.3. Given the mechanism of action of the drug, there are no concerns regarding drug abuse potential, withdrawal or rebound.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

FAERS

A FAERS search was conducted by the Agency. In total, 32 pediatric patients with AEs after exposure to fondaparinux were identified (see table below). The majority of AEs appear related to the underlying disease or were a known adverse reaction (i.e., bleeding) described in the product label. Interpretation of this post-marketing safety data is limited given lack of detailed narratives; however, no new safety signals were identified.

Table 29. FAERS Search

Patient ID	Reason for Use	Adverse Event
(b) (6)	Stent Placement; Thrombosis Prophylaxis	Gastrointestinal Injury; Upper Gastrointestinal Hemorrhage
	Glaucoma; Hypercholesterolemia; Phlebitis; Product Used For Unknown Indication; Small Fiber Neuropathy	Paralysis; Burning Sensation; Diarrhea; Musculoskeletal Stiffness; Vertigo; Headache; Intra-Abdominal Hematoma; Paraesthesia

Patient ID	Reason for Use	Adverse Event
(b) (6)	Embolism Venous	Hematuria; Anemia; Intentional Product Misuse
	Stent Placement; Thrombosis Prophylaxis	Gastrointestinal Injury; Upper Gastrointestinal Hemorrhage
	Acute Myocardial Infarction	Upper Gastrointestinal Hemorrhage; Esophagitis; Gastric Ulcer
	Stent Placement; Thrombosis Prophylaxis	Upper Gastrointestinal Hemorrhage; Gastrointestinal Injury
	Antithrombin III Deficiency	Anomalous Pulmonary Venous Connection; Fetal Exposure During Pregnancy; Heart Disease Congenital
	Anxiety; Product Used For Unknown Indication; Stress	Intentional Self-Injury
	Superficial Vein Thrombosis	Loss Of Consciousness; Pain; Heart Rate Irregular; Dyspnea; Chest Pain; Malaise
	Thrombosis Prophylaxis	Hematemesis; Gastrointestinal Hemorrhage; Pneumonia; Anemia; Respiratory Failure; Melaena
	Cerebrovascular Accident; Prophylaxis; Thrombosis Prophylaxis	Hypovolemic Shock; Hemoglobin Decreased; Hematuria
	Thrombosis Prophylaxis	Hematoma; Superinfection
	Back Pain; Cardiovascular Event Prophylaxis; Infarction; Product Used For Unknown Indication	Shock Hemorrhagic; Gastroduodenal Ulcer; Drug Interaction
	Thrombosis Prophylaxis	Anemia; Melena; Hypovolemic Shock
	Thrombosis	Post Procedural Hemorrhage; Hematoma
	Anticoagulant Therapy; Product Used For Unknown Indication; Arthritis	Dehydration; Pulmonary Thrombosis; Syncope
	Fungal Infection; Product Used For Unknown Indication; Wound Treatment	Drug Reaction With Eosinophilia And Systemic Symptoms; Alopecia; Erythema; Dermatitis Exfoliative Generalized; edema
	Prophylaxis; Superficial Vein Thrombosis	Superficial Vein Thrombosis; Off Label Use; Injection Site Hemorrhage
	Back Pain; Cardiovascular Event Prophylaxis; Infarction; Product Used For Unknown Indication	Drug Interaction; Gastroduodenal Ulcer; Pulmonary Embolism; Shock Hemorrhagic
	Product Used For Unknown Indication; Thrombosis Prophylaxis	Intra-Abdominal Hematoma; Physical Deconditioning; Pleural Effusion; Renal Hemorrhage; Abdominal Mass; Weight Decreased; Overdose; Product Quality Issue
	Back Pain; Cardiovascular Event Prophylaxis; Infarction; Product Used For Unknown Indication	Pulmonary Embolism; Drug Interaction; Shock Hemorrhagic; Gastroduodenal Ulcer
	Back Pain; Cardiovascular Event Prophylaxis; Infarction; Product Used For Unknown Indication	Pulmonary Embolism; Gastroduodenal Ulcer; Cardiac Arrest; Shock Hemorrhagic; Drug Interaction
	Product Used For Unknown Indication	Product Dose Omission Issue; Syringe Issue
	Covid-19 Immunization; Pulmonary Embolism	Lymphadenopathy; Breast Hematoma

Patient ID	Reason for Use	Adverse Event
(b) (6)	Acute Coronary Syndrome	Death
	Product Used For Unknown Indication	Headache; Confusional State; Hyponatremia; Drug Interaction; Loss of Consciousness; Hematuria
	Thrombosis Prophylaxis	Pulmonary Embolism; Hemorrhage Intracranial
	Myocardial Infarction; Pain	Esophageal Candidiasis; Cerebral Hemorrhage
	Product Used for Unknown Indication	Red Blood Cell Count Decreased; Condition Aggravated; Hemorrhage; Spontaneous Hematoma
	Product Used for Unknown Indication	Hospitalization
	Thrombosis Prophylaxis	Hemorrhage
	Not reported	Venous Thrombosis Limb

Source: Clinical Reviewer

Global Post-Marketing Safety Reporting

The Agency requested the Applicant provide their global post-marketing safety reporting data for pediatric patients exposed to Arixtra. The Applicant reported there are 14,881 cases of fondaparinux retrieved cumulatively until 30-Nov-2024 from the global safety database, out of which there were 190 pediatric cases.

The Applicant provided the listing of cases which was reviewed by the Agency. The Agency inquired further regarding a case of drug-induced liver injury (DILI) and a separate case of anaphylaxis. The case labeled DILI by the Applicant was a 4-year-old patient (Case number (b) (6) with left axillary lymphatic vascular malformation who had been treated with low molecular weight heparin and enoxaparin in the past with no increase in liver enzymes. She then presented with a superficial strawberry hemangioma on the right elbow and left shoulder unresponsive to enoxaparin. Fondaparinux was initiated, off-label, and then the patient presented with fever, abdominal pain and vomiting. At that time, aspartate aminotransferase (AST) was at 720 UI/L, alanine aminotransferase (ALT) was at 509 UI/L, and gamma-GT (GGT) level was at 161 UI/L. Bilirubin was reported as normal. Hepatitis A, B, and C virus, Herpes virus, Cytomegalovirus, Epstein Barr virus, Adenovirus and Enterovirus serologies were negative. Treatment with fondaparinux sodium was discontinued, and treatment with enoxaparin was reintroduced. Liver enzymes tests normalized.

Clinical reviewer comment: *Liver enzyme increase is an adverse reaction described in the adult population. This risk is also present in the pediatric population. Upon further inquiry, the patient appeared to have hepatic enzyme increase (<10x ULN) and did not meet criteria for DILI as the bilirubin is normal. It is very likely that fondaparinux led to the liver enzyme increase in this patient given the timing of the event in relation to fondaparinux administration and the positive dechallenge. The Applicant states 2 cases of liver enzyme increase >10 ULN have been reported in their global safety database in pediatric patients.*

To describe this risk, Section 6.2 Postmarketing Experience in the label will state that elevations of hepatic transaminases have been reported in pediatric patients with elevations greater than 10x ULN. In section 6.1, abnormal liver function is included in described adverse events.

The Applicant also provided two case narratives of anaphylaxis as requested by the Agency. First, a 16-year-old patient (Case number (b) (6)) with an anaphylactic reaction was being treated, off-label, for deep venous thrombosis prophylaxis. The patient's medical history included latex allergy, asthma, and iodine allergy. Four days following the fondaparinux administration, a significant anaphylactic reaction reportedly occurred with malaise and breathlessness. The patient was managed in the emergency room. Fondaparinux was discontinued, and the event of anaphylactic reaction resolved. No co-suspect medications or concomitant medications were provided. In the second case of anaphylaxis identified by the Applicant (case number (b) (6)), fondaparinux given for thrombosis prophylaxis in an adolescent patient while undergoing treatment for fracture of the lateral ankle. The patient reportedly experienced circulatory collapse on the first day after receiving fondaparinux. The patient also had a long waiting time during hot weather and stood suddenly at the time of collapse. There was limited information on concomitant medications. Afterwards, the patient had four weeks of treatment with fondaparinux with no complications.

Clinical reviewer comment: *Both cases of anaphylaxis are clearly unrelated to fondaparinux. The first anaphylactic reaction is confounded by the patient's history of asthma and allergies to latex and iodine. In addition, the reaction occurred four days after the administration of fondaparinux making the reaction unlikely due to the drug. The second case of suspected anaphylaxis was unlikely related to the drug as the patient went on to receive four more weeks of the drug with no further sequelae. Of note, anaphylaxis has occurred in the adult population and is listed as an adverse reaction in Section 6.2 of the USPI.*

8.9.2. Expectations on Safety in the Postmarket Setting

Safety in the postmarket setting is expected to be similar to that observed in the clinical study reviewed in this application and what is known from adult and pediatric post marketing safety data.

8.9.3. Additional Safety Issues from Other Disciplines

Division of Medication Error Prevention and Analysis (DMEPA) performed a risk assessment of the proposed Arixtra Prescribing Information (PI), Patient Package Insert (PPI) and Instructions for Use (IFU) to identify deficiencies that may lead to medication errors and other areas of improvement, see finalized review in DARRTS dated November 14, 2024. This included evaluating the risks associated with pharmacy repackaging patient specific doses for outpatient use. The repackaging approach outlines a pharmacist transferring the full contents of a commercially available PFS into an empty sterile vial, then withdrawing the required dose into

an empty graduated syringe which will be stored for a certain amount of time and administered at home. Individual pharmacy prepared syringes up to a month supply would be dispensed for administration at home.

DMEPA had concerns with including instructions in the labeling that describe the preparation of individual pediatric doses from a single-dose prefilled syringe for dispensing as manipulation of the device for preparation of other doses increases the risk of medication errors (e.g. underdose/overdose). Additional concerns included dosing accuracy, sterility of the drug product due to an increased number of manipulations required to transfer to the final syringe (e.g., transfer from PFS to vial, from vial to a second syringe, recapping the needle), stability between the drug product and supplies used during preparation (e.g., syringes, vials, needles), and potential for variability in practices and supplies at each pharmacy which may further contribute to sterility and stability concerns.

DMEPA also was concerned that the Applicant did not develop a readily available pediatric presentation to fulfill PREA and that the current approach for dosing for patients between 10-20kg may increase medication errors. While the clinical team agrees that a pediatric presentation for patients between 10-20kg is preferred, the pediatric population that requires this product is small and there remains an unmet medical need in this population for this treatment. The revised labeling will include detailed preparation instructions for the individual pediatric doses from a single-dose prefilled syringe. The risk of medication errors can be mitigated through labeling and the benefit/risk profile of Arixtra for pediatric patients remains favorable.

The Applicant proposed that for pediatric patients weighing greater than 20 kg the dose be rounded to the nearest prefilled syringe and for pediatric patients weighing 10 kg to 20 kg the dose be rounded to the nearest 0.1 mg, this raised the concern for dosing accuracy. The clinical team believes the risk of harm is low if an exact dose is not measured as patients are monitored closely and doses adjusted based on anti-Xa levels and thus the dose is adjusted to a safe and therapeutic range. The review team determined that the proposed rounding approach is acceptable.

Risks with sterility were addressed in labeling, which included providing instructions for the pharmacy with aseptic technique. In addition, DMEPA discussed concerns regarding sterility and stability with OPQ. OPQ confirmed they have no approvability/stability issues with the use of a tuberculin syringe for preparation of Arixtra and revised the PI accordingly.

8.10. Integrated Assessment of Safety

In total, 366 patients were evaluated for safety after exposure to fondaparinux. This safety database is adequate given the rarity of VTE in the pediatric population. Bleeding is a common and serious adverse reaction associated with all anticoagulants. Overall, major and clinically

relevant nonmajor bleeding events were low in pediatric patients exposed to fondaparinux, supporting the conclusion of safe use of this drug. Assessment of other toxicities related to fondaparinux was limited given the prespecified selection of adverse events of special interest and the rates of select adverse events were low. To further assess safety, a search of the Applicant's global safety database, literature and FAERS database was conducted. The Applicant's global safety database identified 2 cases of liver enzyme increase >10x ULN, this will be added to the postmarketing section of the UPSI. Overall, the risk profile appears acceptable for pediatric patients.

9. Advisory Committee Meeting and Other External Consultations

An advisory committee meeting was not convened to discuss this application. No issues were identified that would have benefitted from a public discussion with external experts.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Summary of Significant Labeling Changes (High Level Changes)		
Section	**Proposed Labeling**	**Approved Labeling**
Highlights, Indications and Usage	The Applicant proposed the following indication: (b) (4)	The Agency revised the indication to: Treatment of venous thromboembolism (VTE) in pediatric patients aged 1 year or older weighing at least 10 kg.
Dosage and Administration (2.5 and 2.8)	The Applicant proposed dosing (b) (4)	The Agency made revisions for clarity, and in particular, highlighted that for patients weighing 10 kg to 20 kg, the recommended initial dose is 0.1 mg/kg subcutaneously once daily. There is no available prefilled syringe for patients in this weight range. Additional instructions for dose preparation were provided for the pharmacy in 2.8.
Adverse Reactions (6.1 and 6.2)	The Applicant added pediatric bleeding adverse reactions to the label.	In addition to bleeding adverse reactions the Agency added other adverse reactions that occurred during treatment with fondaparinux sodium

Summary of Significant Labeling Changes (High Level Changes)		
Section	**Proposed Labeling**	**Approved Labeling**
		injection in pediatric studies included: anemia, thrombocytopenia, generalized skin associated events, abnormal liver function, hypokalemia, and decreased blood pressure. Per the Agency recommendation, liver enzyme increase >10x ULN was added to the postmarketing safety section of the label for pediatric patients.
Pediatric Use (8.4)	The Applicant updated the Pediatric Use section to include pediatric data.	The Agency added the following statement: The safety and effectiveness of Arixtra have not been established in pediatric patients for the prophylaxis of DVT and treatment of DVT or PE in conjunction with warfarin sodium.
Special Populations (12.4)	The Applicant added pediatric information.	The Agency updated for clarity.
Clinical Studies (14.8)	The Applicant added pediatric efficacy data based on the efficacy analysis set of (b) (4) patients.	The Agency (b) (4) requested the Applicant update the results to reflect a total of 325 patients.

11. Risk Evaluation and Mitigation Strategies (REMS)

A REMS is not necessary for fondaparinux. All safety issues can be adequately managed through labeling.

12. Postmarketing Requirements and Commitments

This submission addressed two PREA PMRs:
PMR 2151-1: Deferred pediatric study under PREA for the treatment of acute deep vein thrombosis when administered in conjunction with warfarin sodium in pediatric patients ages one to 16 years.

PMR 2151-2 Deferred pediatric study under PREA for the treatment of acute pulmonary embolism when administered in conjunction with warfarin sodium in pediatric patients ages one to 16 years.

The study conducted addressed the drug alone rather than what the PREA PMRs described, which were for the drug to be studied together with warfarin. It is not practical or ethical to conduct a study in pediatric patients with VTE in which Arixtra would be given in conjunction with warfarin. While this approach is used in adults, it is not standard practice in pediatric patients and can lead to increased risk of serious bleeding.

The data from Study 7001 are sufficient to inform labeling of Arixtra for use in pediatric patients aged 1 year or older and therefore the Division has determined the PREA PMRs are fulfilled. The Division met with Pediatric Review Committee (PeRC) on October 22, 2024 and PeRC agreed the PREA PMRs have been fulfilled.

No new PMRs or PMCs are recommended with this submission.

13. Appendices

13.1. References

1. Mahajerin A, Croteau SE. Epidemiology and Risk Assessment of Pediatric Venous Thromboembolism. Front Pediatr. 2017 Apr 10;5:68. doi: 10.3389/fped.2017.00068. PMID: 28443269; PMCID: PMC5385336.
2. Witmer, C. and L. Raffini, *Treatment of venous thromboembolism in pediatric patients.* Blood, 2020. 135(5): p. 335-343.
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4. Smith, R., S. Jones, and F. Newall, *Six Weeks Versus 3 Months of Anticoagulant Treatment for Pediatric Central Venous Catheter-related Venous Thromboembolism.* J Pediatr Hematol Oncol, 2017. 39(7): p. 518-523.
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6. Mitchell LG, Goldenberg NA, Male C, Kenet G, Monagle P, Nowak-Göttl U; Perinatal and Paediatric Haemostasis Subcommittee of the SSC of the ISTH. Definition of clinical efficacy and safety outcomes for clinical trials in deep venous thrombosis and pulmonary

embolism in children. J Thromb Haemost. 2011 Sep;9(9):1856-8. doi: 10.1111/j.1538-7836.2011.04433.x. PMID: 21884565.

7. Young G, Yee DL, O'Brien SH, Khanna R, Barbour A, Nugent DJ. FondaKIDS: a prospective pharmacokinetic and safety study of fondaparinux in children between 1 and 18 years of age. Pediatr Blood Cancer. 2011 Dec 1;57(6):1049-54. doi: 10.1002/pbc.23011. Epub 2011 Feb 11. PMID: 21319285.

13.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): FDPX-IJS-7001

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 1		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		

Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

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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